(19) Europäisch s Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: 0 337 549 A1

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 89200864.0

(51) Int. Cl.⁴: C07D 205/08 , A61K 31/395

(22) Date of filing: 06.04.89

(30) Priority: 11.04.88 US 179688

(43) Date of publication of application:
18.10.89 Bulletin 89/42

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(71) Applicant: MERCK & CO. INC.
126, East Lincoln Avenue P.O. Box 2000
Rahway New Jersey 07065-0900(US)

(72) Inventor: Shah, Shrenik K.
25 Denise Court
Metuchen New Jersey 08840(US)
Inventor: Finke, Paul E.
34 Inwood Drive
Milltown New Jersey 08850(US)
Inventor: Doherty, James B.
559 Columbia Street
New Milford New Jersey 07646(US)
Inventor: Barker, Peter L.
518 Hort Street
Westfield New Jersey 07090(US)
Inventor: Hagmann, William
309 Hyslip Avenue
Westfield New Jersey 07090(US)
Inventor: Dorn, Conrad P.
972 Fernwood Avenue
Plainfield New Jersey 07062(US)
Inventor: Firestone, Raymond A.
387 Temple Street
New Haven Connecticut 06511(US)

(74) Representative: Hesketh, Alan, Dr.
European Patent Department Merck & Co., Inc. Terlings Park Eastwick Road
Harlow Essex, CM20 2QR(GB)

(54) New substituted azetidinones as anti-inflammatory and antidegenerative agents.

(57) New substituted azetidinones are found to be potent elastase inhibitors and thereby useful anti-inflammatory/antidegenerative agents.

NEW SUBSTITUTED AZETIDINONES AS ANTI-INFLAMMATORY AND ANTIDEGENERATIVE AGENTS

BACKGROUND OF THE INVENTION

We have found that a group of new substituted azetidinones are potent elastase inhibitors and therefore are useful anti-inflammatory/antidegenerative agents.

Proteases from granulocytes and macrophages have been reported to be responsible for the chronic tissue destruction mechanisms associated with inflammation, including rheumatoid arthritis and emphysema. Accordingly, specific and selective inhibitors of these proteases are candidates for potent anti-inflammatory agents useful in the treatment of inflammatory conditions resulting in connective tissue destruction, e.g. rheumatoid arthritis, emphysema, bronchial inflammation, osteoarthritis, spondylitis, lupus, psoriasis, atherosclerosis, sepsis, septicemia, shock, periodontitis, cystic fibrosis and acute respiratory distress syndrome.

The role of proteases from granulocytes, leukocytes or macrophages are related to a rapid senes of events which occurs during the progression of an inflammatory condition:

(1) There is a rapid production of prostaglandins (PG) and related compounds synthesized from arachidonic acid. This PG synthesis has been shown to be inhibited by aspirin-related nonsteroidal anti-inflammatory agents including indomethacin and phenylbutazone. There is some evidence that protease inhibitors prevent PG production;

(2) There is also a change in vascular permeability which causes a leakage of fluid into the inflam d site and the resulting edema is generally used as a marker for measuring the degree of inflammation. This process has been found to be induced by the proteolytic or peptide cleaving activity of proteases, especially those contained in the granulocyte, and thereby can be inhibited by various synthetic proteas inhibitors, for example, N-acyl benzisothiazolones and the respective 1,1-dioxides. Morris Zimmerman et al., J. Biol. Chem., 255, 9848 (1980); and

(3) There is an appearance and/or presence of lymphoid cells, especially macrophages and polymorphonuclear leukocytes (PMN). It has been known that a variety of proteases are released from th macrophages and PMN, further indicating that the proteases do play an important role in inflammation.

In general, proteases are an important family of enzymes within the peptide bond cleaving enzymes whose members are essential to a variety of normal biological activities, such as digestion, formation and dissolution of blood clots, the formation of active forms of hormones, the immune reaction to foreign cells and organisms, etc., and in pathological conditions such as the degradation of structural proteins at th articular cartilage-pannus junction in rheumatoid arthritis etc.

Elastase is one of the proteases. It is an enzyme capable of hydrolyzing the connective tissue component elastin, a property not contained by the bulk of the proteases present in mammals. It acts on a protein's nonterminal bonds which are adjacent to an aliphatic amino acid. Neutrophil elastase is of particular interest because it has the broadest spectrum of activity against natural connective tissu substrates. In particular, the elastase of the granulocyte is important because, as described above, granulocytes participate in acute inflammation and in acute exacerbation of chronic forms of inflammation which characterize many clinically important inflammatory diseases.

Proteases may be inactivated by inhibitors which block the active site of the enzyme by binding tightly thereto. Naturally occurring protease inhibitors form part of the control or defense mechanisms that are crucial to the well-being of an organism. Without these control mechanisms, the proteases would destroy any protein within reach. The naturally occurring enzyme inhibitors have been shown to have appropriate configurations which allow them to bind tightly to the enzyme. This configuration is part of the reason that inhibitors bind to the enzyme so tightly (see Stroud, "A Family of Protein-Cutting Proteins" Sci. Am. July 1974, pp. 74-88). For example, one of the natural inhibitors, α_1 -Antitrypsin, is a glycoprotein contained in human serum that has a wide inhibitory spectrum covering, among other enzymes, elastase both from the pancreas and the PMN. This inhibitor is hydrolyzed by the proteases to form a stable acyl enzyme in which the activ site is no longer availabl . Mark d reduction in serum α_1-antitrypsin, either genetic or due to oxidants, has been associated with pulmonary emphysema which is a disease characterized by a progressiv loss of lung elasticity and resulting respiratory difficulty. It has been reported that this loss of lung elasticity is caused by the progressive, uncontrolled proteolysis or destruction f the structur of lung tissue by prot ases such as elastase released from leukocytes. J. C. Powers, TIBS, 211 (1976).

Rh umatoid arthritis is characterized by a progressive destruction of articular cartilage both on th free

surface bordering the joint space and at the erosion front built up by synovial tissue toward the cartilage. This destruction process, in turn, is attributed to the protein-cutting enzyme elastase which is a neutral protease present in human granulocytes. This conclusion has been supported by the following observations:

(1) Recent histochemical investigations show d the accumulation of granulocytes at the cartilage/pannus junction in rheumatoid arthritis; and

(2) a recent investigation of mechanical behavior of cartilage in response to attack by purified elastase demonstrated the direct participation of granulocyte enzymes, especially elastase, in rheumatoid cartilage destruction. H. Menninger et al., in Biological Functions of Proteinases, H. Holzer and H. Tschesche, eds. Springer-Verlag, Berlin, Heidelberg, New York, pp. 196-206, 1979.

Accordingly, an object of this invention is to discover new protease inhibitors, especially elastase inhibitors, useful for controlling tissue damage and various inflammatory or degenerative conditions mediated by proteases particularly elastase.

Another object of the present invention is to provide pharmaceutical compositions for administering the active substituted azetidinones as protease inhibitors especially human leukocyte elastase.

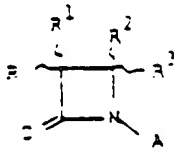
Still a further object of this invention is to provide a method of controlling inflammatory conditions by administering a sufficient amount of one or more of the active, substituted azetidinones in a mammalian species in need of such treatment.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to potent elastase inhibitors of formula (I) which are useful in the prevention, control and treatment of inflammatory/degenerative conditions especially arthritis and emphysema.

A large number of the azetidinone derivatives of formula (I) are known antibiotics which have been described in patents and various publications.

The formula of the substituted azetidinones which are found to exhibit anti-inflammatory and antidegenerative activities by the present invention are represented as follows:



(I)

wherein

R can be at the α or the β-position and is hydrogen, straight or branched loweralkyl especially C_{1-6}alkyl, such as methyl, ethyl, n- or i-propyl, butyl, pentyl or hexyl; or loweralkyl substituted with a radical R^4 as defined below; or halo such as fluoro, chloro or bromo;

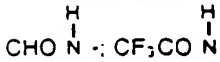
R^1 can be at the α- or the β-position and is

(1) OB or $-S(O)_nB$ wherein B is as defined below and n is 0, 1 or 2;

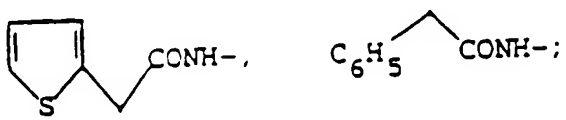
(2) Straight or branched loweralkenyl especially C_{2-3}alkenyl such as vinyl, allyl, $-CH_2CH=C(CH_3)_2$, and $-CH_2CH_2CH=CH_2$;

(3) loweralkyl as defined above;

(4) acylamino e.g.



$CHO\overset{H}{\underset{|}{N}}-$; $CF_3CO\overset{H}{\underset{|}{N}}-$, $CH_3CO\overset{H}{\underset{|}{N}}-$.

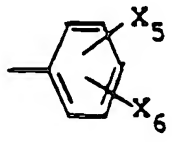


or

(5) amino;

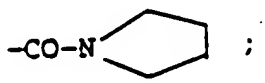
(6) Straight or branched loweralkynyl group especially C_{3-5} alkynyl such as -C≡CH, $-CH_2$-C≡CH and $-CH_2CH_2$-C≡CCH_3;

(7) An aryl group having 6-14 carbon atoms as described below such as ph nyl of formula



wherein X_5 and X_6 independently are:

1) Q, where Q is H, loweralkyl, haloloweralkyl, phenyl or substituted phenyl as previously defined, or naphthyl;
2) halo,
3) loweralkenyl;
4) loweralkynyl;
5) -SQ;
6) -OQ;
7) -CHQCOQ', where Q' is defined as Q and Q' can be the same as or different from Q;
8) -CHQCOOQ' such as CH_2COOH;
9) $-CH_2SQ$;
10) -CHQSQ';
11) $-CH_2OQ$ or -CHQOQ' especially $-CH_2OH$ and $-CH_2OCH_3$;
12) -COQ for example, $-COCH_3$ and -(CO)H;
13) -COOQ especially -COOH and COOt-Bu;
14) -OCOQ such as $-OCOCH_3$;
15) -NQQ';
16) -NQCOQ' especially $-NHCOCH_3$;
17) $-CH_2$ NH_2 or $-CH_2\overset{+}{N}(CH_3)_3I^-$;
18) $-CH_2OCOCH_3$;
19) $-NQSO_2Q'$;
20) $-SO_2NQQ'$;
21) -SOQ;
22) $-SO_2Q$;
23) $-SO_3Q$;
24) -CN;
25) $-NO_2$;
26) -CONQQ';
27) -NO;
28) -CSQ;
29) -CSNQQ';
30) $-CF_2SQ$;
31) $-CF_2OQ$;
32) -NQCONHQ' or NQCONQ'Q^2 where Q^2 is defined as Q' and Q^2 can be the same as or different from Q';
33) $-CH_2Y$ wherein Y represents -CH(NHAC)COO^-, $CH(\overset{+}{N}H_3)$ COO^-, CH_2COOH, COOH, $-N(CH_3)_2$, OH, $CH_2N(CH_3)_2$, or CH_2OH;
34) -CH(C$_{1-5}$ alkyl);
35) $-NH(CO)CH_2CH_2COOH$;
36)



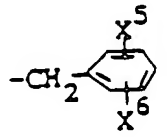
;

or

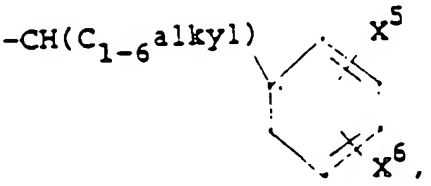
37) -CO-NH-SO_2ph nyl or substituted ph nyl such as p-chlorophenyl;

8) heteroaryl such as unsubstituted or substituted furyl, thienyl, thiazolyl, pyrryl, pyrimidinyl, pyridyl, oxazolyl, tetrazolyl or imidazolyl wherein the substituents are as those described for substituted phenyls;

9) aralkyl especially phenyl C_{1-5}alkyl such as benzyl of formula



or



or phenethyl;

(10) halo such as F, Cl, Br or I;

(11) N_3;

(12) hydrogen;

(13) R and R' may join together and form a cycloalkyl such as a C_{1-5}cycloalkyl, e.g., cyclopentane, $=C(B)(B_1)$ or =O (oxo) wherein B and B_1 independently are as defined below;

(14) $-CH_2OC_{1-5}$ alkyl especially $-CH_2OCH_3$ and $-CH_2OC_2H_5$;

(15) $-CH_2CH_2OC_{1-5}$alkyl especially $-CH_2CH_2OC_2H_5$;

R^2 and R^3 can be at the α or the β-position and independently are

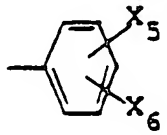
(1) B as defined below;

(2) -CONBB' wherein B and B' independently represent

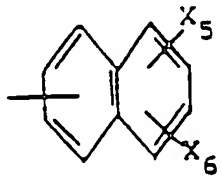
(a) H;

(b) straight or branched alkyl having from 1 to 20 carbon atoms, preferrably C_{1-5}alkyl such as methyl, ethyl, isopropyl, t-butyl, pentyl or hexyl;

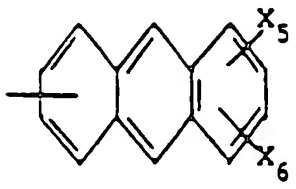
(c) aryl having from 6 to 14 carbon atoms such as phenyl or substituted phenyl of formula



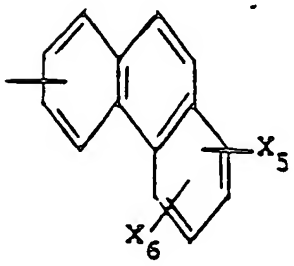
naphthyl or substituted naphthyl of formula



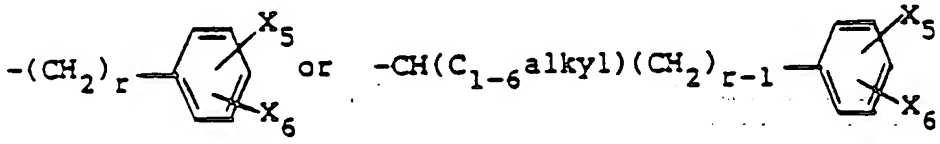
or anthracyl or substituted anthracyl of formula



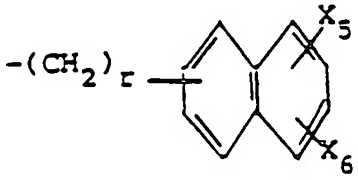
or



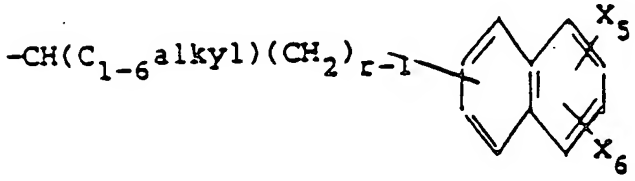
(d) cycloalkyl having from 3 to 8 carbon atoms especially cyclopropyl, cyclopentyl or cyclohexyl;
(e) straight or branched alkenyl having from 2 to 20 carbon atoms, for example, allyl;
(f) straight or branched alkynyl having from 2 to 20 carbon atoms, for example, -C≡CH;
(g) aralkyl, alkaryl, aralkenyl, aralkynyl, alkenylaryl or
alkynylaryl wherein alkyl, aryl, alkenyl and alkynyl are as previously defined for example, C_{1-6}alkylphenyl of formula



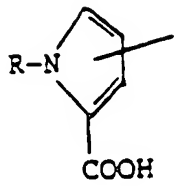
wherein r is 1 to 6, C_{1-6}alkyl naphthyl of formula



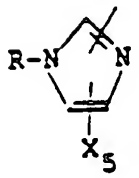
or



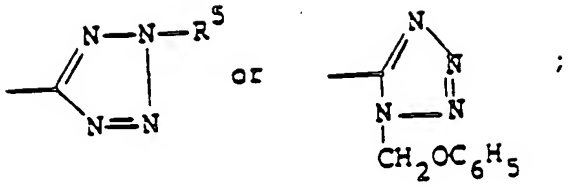
(h) heteroaryl comprising monoheteroaryl, di- or polyheteroaryl, or fused heteroaryl containing from 1 to 3 of any one or more of th heteroatoms N, S or O in each heteroaryl ring thereof, for example, pyridyl, pyrryl, such as



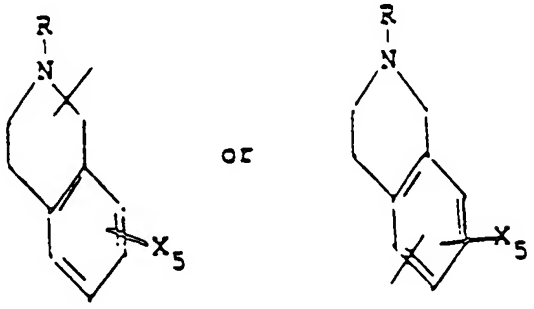
thienyl, isothiazolyl, imidazolyl such as



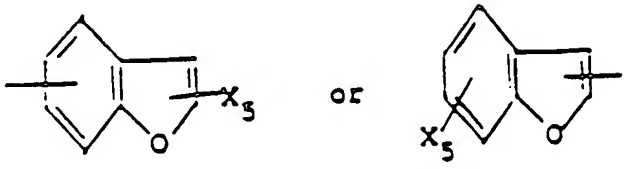
tetrazolyl such as



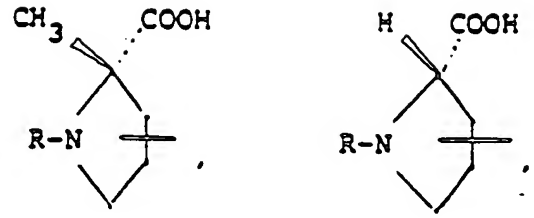
pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, tetrahydroisoquinolyl such as



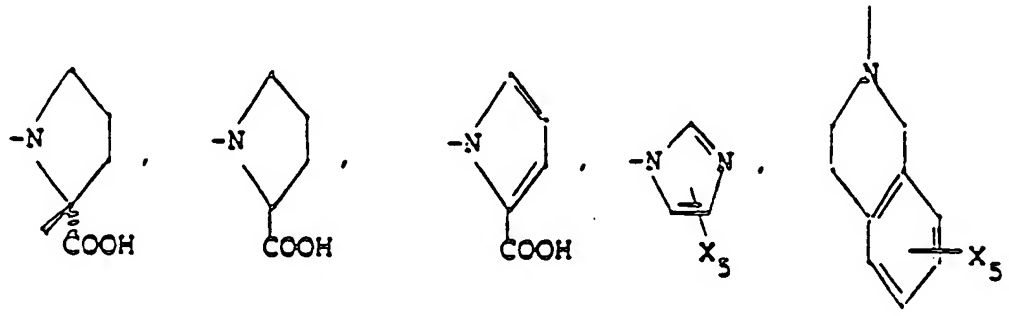
benzothienyl, benzofuryl such as



pyrazolyl, indolyl, purinyl, carbazolyl, isoxazolyl and the like:
(i) heteroarylalkyl such as 2-pyridylmethyl, 2-thienylmethyl and 3-isothiazolylethyl; or
(j) heterocycloalkyl e.g., 1,3-dioxacycloh x-4-yl, piperidino.

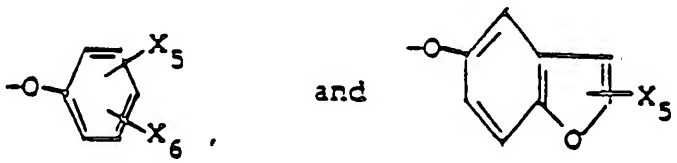


morpholino, oxacyclopropyl, pyrrolidino, benzothiazolino, imidazolidino, pyrazolidino, and piperazino;
(k) heterocycloalkenyl such as pyrrolino, 2-imidazolino, 3-pyrazolino or isoindolino;
(l) B and B_1 joined together and form a heterocyclic ring containing at least one N-atom and optionally 1 to 3 of the heteroatoms, N, S, or O, e.g.,



the above groups (a)-(l) can be unsubstituted or can be substituted by one or more radical R^4 selected from the group consisting of loweralkyl, hydroxy, aryloxy (OAr), alkoxy, halo, nitro, loweralkylthio, arylthio, mercapto, amino, monoalkyl or dialkyl substituted amino, cyano, carboxy, loweralkanoyl, Ar(C = O), aminosulfonyl, aminosulfenyl, aminosulfinyl, carbamoyl, carbamoyloxy, $-S(O)_nR^5$, SO_3R^5, $-P(O)_qR^5$ (where q is 1 or 2 and R^5 is H, C_{1-5} alkyl, aralkyl or aryl as previously defined), azido, carboxamido or N-substituted carboxamido;

(3) $-S(O)_nB$;
(4) $-S(O)_nNBB_1$;
(5) $-N(B)S(O)_nB_1$;
(6) $-P(O)_qBB_1$;
(7) -C(O)B especially acetyl, benzoyl, e.g., p-chlorobenzoyl, p-methylbenzoyl and p-aminosulfonylbenzoyl;
(8) -OB especially $-OC_{1-6}$alkyl, phenoxy or substituted phenoxy of formula



(9) -COOB, -OC(O)OB or OC(O)NBB$_1$;
(10) -O-C(O)-B especially C_{1-5}alkanoyloxy such as acetyloxy;
(11) cyano;
(12) -S-C(O)-B especially C_{1-6}alkanoylthio such as acetylthio; or
(13) R^2 and R^3 may join and form $=C(B_1)(B)$, a C_{1-5}cycloalkyl for example, cyclopentyl, and =O-(OXO);

A is
(1) -O-C(O)-B;
(2) $-S(O)_nB$;
(3) $-S(O)_nNBB_1$;

(4) -C(O)B;

(5) SO_3-M^+ wherein M represents

(a) an alkali anion such as Na^+, K^+; or

(b) a quaternary ammonium group of formula $N^+(R^5)_4$, for example, $(n\text{-}Bu)_4N^+$;

(6) substituted or unsubstituted phosphoryl or phosphonyl such as $-P(O)_3(R^5)_2$ or $-P(O)_4R^5$;

(7) $-C(O)NBB_1$ especially $-CON(C_2H_5)$Phenyl and -CONHB:, wherein B_1 is

(a) $-(CH_2)_r$ Ph, or $CH(C_{1-6}alkyl)(CH_2)_{r-1}$Ph, e.g., $-CH(C_2H_5)$-Ph, $-CH(C_3H_7)$-Ph, -CH-(allyl)-Ph, $-CH(C_2H_5)$-CH_2Ph, or $-CH(CH_3)$-Ph wherein Ph represents phenyl or substituted phenyl as previously defined, for examples, 4-methyl-phenyl, 4-methoxyphenyl, 4-N,N-dimethyl-amino-phenyl, 4-benzyloxy-phenyl, 4-phenyl-phenyl, 3,4-methylenedioxy-phenyl, and 3,4-dimethyl-phenyl;

(b) $-(CH_2)_r$(Naph) especially $-CH_2$(Naph) or $-CH(C_2H_5)$(Naph) wherein (Naph) is α or β-naphthyl or substituted naphthyl as previously defined;

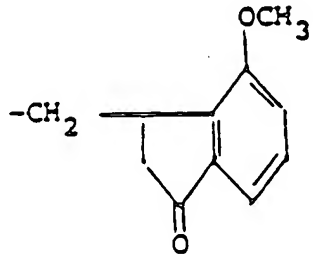
(c) $-(CH_2)_r$(Ar) especially $-CH_2CH_2Ar$ or $-CH_2Ar$ wherein Ar represents heteroaryl especially 2-thienyl, 2-furyl, 3-thienyl, or benzofuryl;

(d) $-(CH_2)_r$OPh especially $-CH_2CH_2CH_2OPh$;

(e) $-(CH_2)_r$CH(OH)Ph;

(f) $-(CH_2)_r$(CO)Ph;

(g)



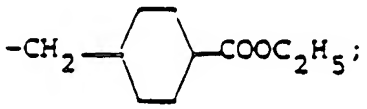
;

(h)

;

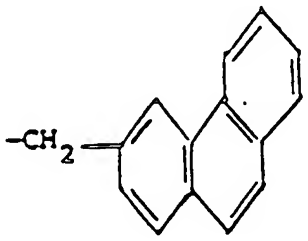
(i) $-CH_2$-Ph(p-CO-NH-SO_2-Ph(p-Cl));

(j)



;

(k)



;

or

(l) -$CH(CH_3)$-Ph(p-cyclohexyl);

(8) -C(O)OB especially C_{1-6} alkoxycarbonyl, .g., methoxycarbonyl, and -ethoxycarbonyl or C $OOCH_2$-Ph(p-$COOC_2H_5$);

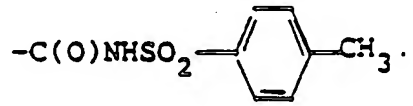
(9) halo C_{1-6}alkyl such as trifluoromethyl;

(10) -OB especially -O-CH_2-(phenyl or substituted phenyl as previously defined), for example, -$OCH_2C_6H_5$; -$OCH_2C_6H_4$-OCH_3; or $OCH_2C_6H_4NO_2$;

(11) silyl such as -$Si(CH_3)_2$(t-Bu);

(12) B especially H, C_{1-6} alkyl, CH_2OH, -$CH_2O(CO)CH_3$, phenyl or substituted phenyl, -CHR^5L where R^5 is as previously defined and L is a good leaving group comprising OAc, SAc, halogen, OR^5, SR^5, SOR^5, SO_2R^5, OTs, $OCOCF_3$, and mesyl wherein Ac is acetyl; and Ts is tosyl; or

(13)



Preferably, the compounds of the present invention are of formula (I) wherein:

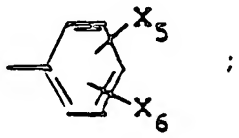
R is hydrogen; or C_{1-6}alkyl;

R^1 is

(1) C_{1-6} alkyl especially methyl or ethyl

(2) OR^5;

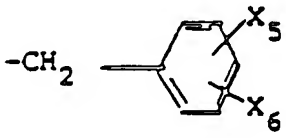
(3) phenyl of formula



;

(4) hydrogen;

(5) benzyl of formula



(6) CH_2OC_{1-6}alkyl or -$CH_2CH_2OC_{1-6}$ alkyl;

(7) C_{2-8} alkenyl; or

(8) R and R^1 may join together and form a cyclopentane;

R^2 and R^3 independently are

(1) hydrogen;

(2) $S(O)_nR^5$;

(3) COOB;

(4) $CONBB_1$;

(5) OB;

(6) C_{1-6} alkyl;

(7) phenyl or substituted phenyl as previously defined;

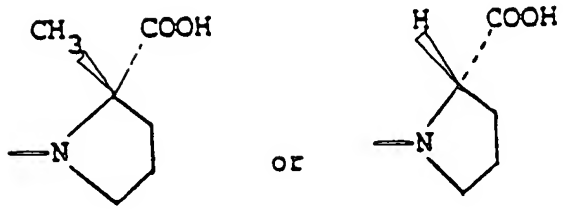
(8) naphthyl as previously defined;

(9) cyclohexyl;

(10) benzyl as previously defined;

(11) heteroaryl selected from a group consisting of imidazolyl, benzofuryl and tetrahydroisoquinolyl;

(12) heterocycloalkyl such as



(13) C(O)B;

A is

(1) SOR^5;

(2) SO_2R^5;

(3) COOB;

(4) C(O)B;

(5) CONBB$_1$, wherein B and B$_1$ independently are;

(a) H;

(b) C_{1-5}alkyl;

(c) -$(CH_2)_r$Ph where r represents 1 or 2 and Ph represents phenyl or substituted phenyl as previously defined;

(d) CH(C_{1-5}alkyl)$(CH_2)_{r-1}$Ph where Ph is as defined above;

(6) phenyl or substituted phenyl as previously defined such as p-methoxyphenyl, p-nitrophenyl and p-methylphenyl;

(7) C_{1-5} alkyl;

(8) CH_2OH;

(9) $CH_2OC(O)CH_3$; or

(10) -$C(O)NHSO_2$-Ph(p-CH_3).

Even more preferably, the compounds of the present invention are of formula (I) wherein

R is hydrogen or C_{1-3}alkyl;

R' is

(1) hydrogen;

(2) C_{1-5}alkyl;

(3) C_{1-5}alkoxy such as methoxy;

(4) C_{2-5}alkenyl;

(5) phenyl or substituted phenyl as previously defined; or

(6) CH_2OC_{1-3} alkyl;

R^2 is hydrogen;

R^3 is

(1) $S(O)_nR^5$;

(2) CONBB$_1$;

(3) COOB;

(4) phenoxy or substituted phenoxy;

(5) imidazolyl; or

(6) substituted or unsubstituted alkoxy, for examples, OCH_3 or -OCH_2CONH_2;

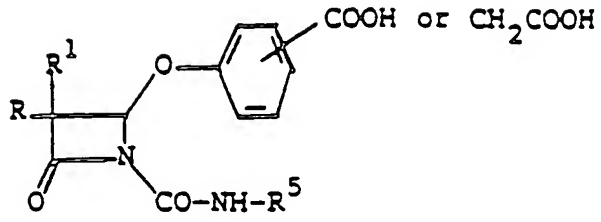
A is

(1) CO_2R^5 wherein R^5 is H, C_{1-5} alkyl, -CH_2Ph, -CH(CH_3)Ph, -CH(C_2H_5)Ph, CH(C_3H_7)Ph or CH-(C_3H_5)Ph wherein Ph represents phenyl or substituted phenyl as previously defined;

(2) $CONHR^5$; or

(3) SO_2R^5.

The most preferred compounds of the present invention are listed in the following table.



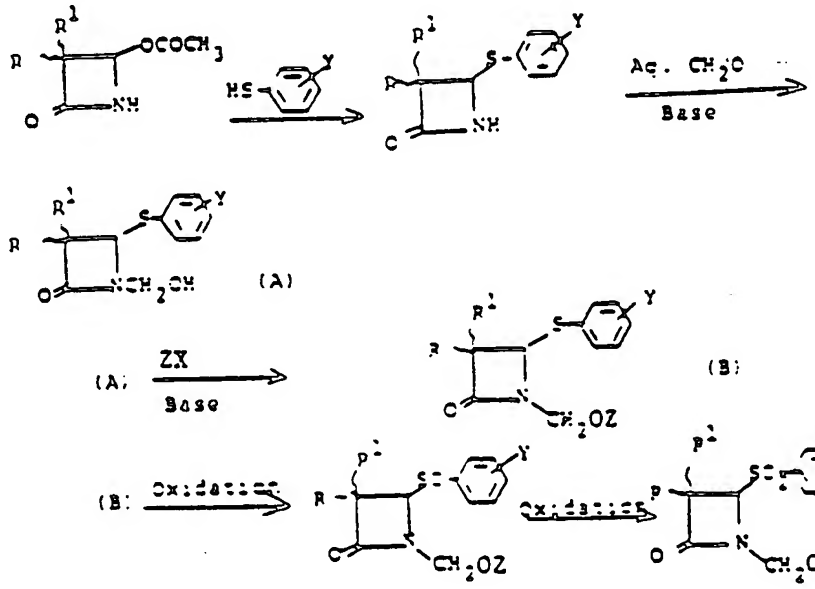
R	R^1	R^5
C_2H_5	CH_3	$CH(CH_3)Ph$
C_2H_5	C_2H_5	CH_2-(4-Ph-Ph)
C_2H_5	CH_3	$CH(C_2H_5)Ph$
C_2H_5	C_2H_5	$CH(C_2H_5)Ph$
C_2H_5	CH_2OCH_3	$CH(C_2H_5)Ph$
C_2H_5	C_2H_5	$CH(C_3H_7)$-(4-CH_3-Ph)
C_2H_5	C_2H_5	$CH(C_3H_5)$-(4-CH_3-Ph)
C_2H_5	C_2H_5	$CH(C_3H_7)Ph$
C_2H_5	C_2H_5	$CH(C_3H_7)$-(3,4-methylenedioxy-Ph)
C_2H_5	C_2H_5	$CH(C_3H_5)$-(3,4-methylenedioxy-Ph)

In the above table, Ph represents phenyl or substituted phenyl as previously defined.

The compounds of the present invention are either known or are prepared among other methods by the following representative schemes.

Scheme (a)

as illustrated by Examples 16-19.



wherein

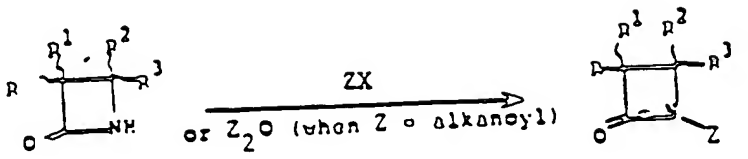
Y is $-NO_2$, $-CH_3$, $-OCH_3$, -Cl, -F, etc;

X is halo, e.g., Cl, Br or I;

Z is BCO or BSO_2.

Scheme (b)

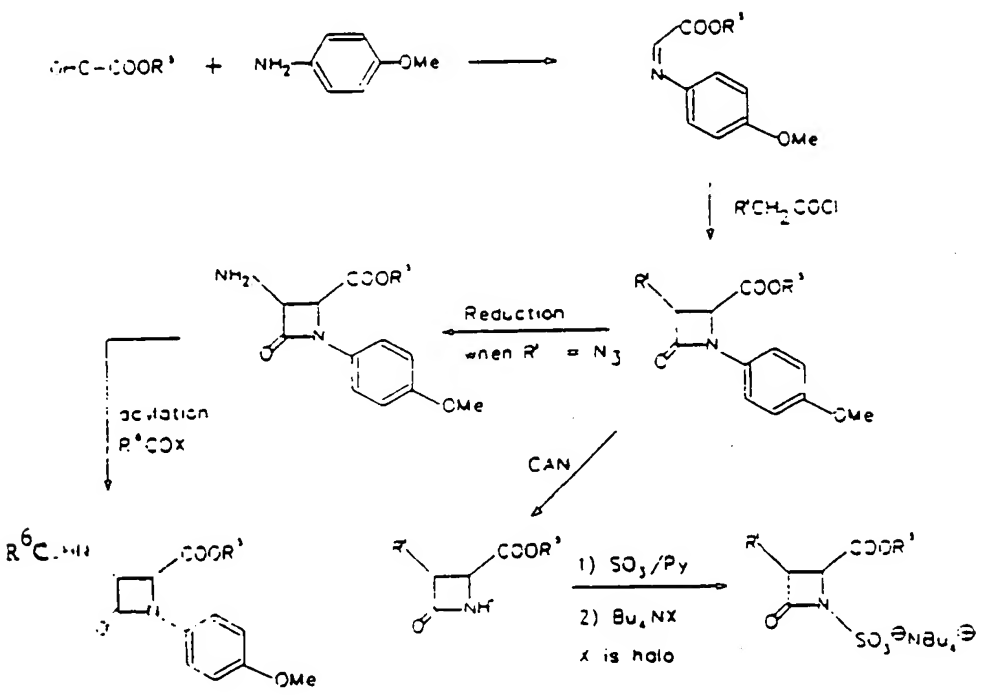
as illustrated by Examples 1-4.



wherein
X is halo;
Z is as previously defined, e.g., $-SO_2-(p-NO_2-Ph)$, $-COCH_3$, $-CH_2OTs$, etc. wherein Ph represents phenyl or substituted phenyl.

Scheme(c)

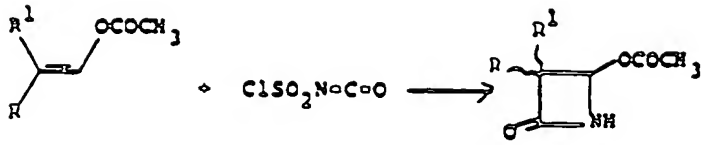
as illustrated by Examples 5-15



wherein
R^6 is H, CF_3, CH_3, etc.;
R^5 and R^1 are as previously defined; and
CAN is cerric ammonium nitrate.

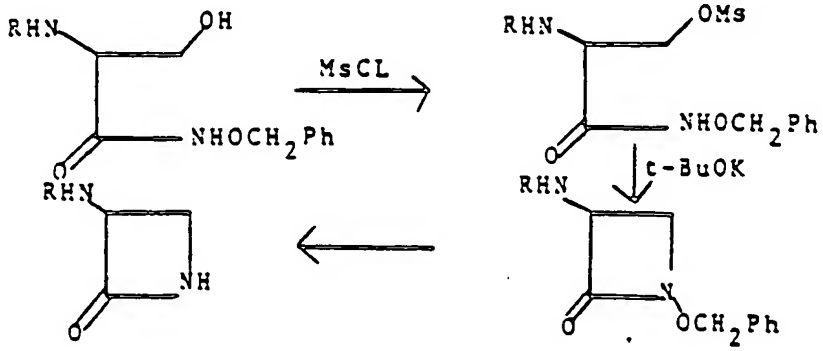
Scheme (d)

as illustrated by Examples 2-3.



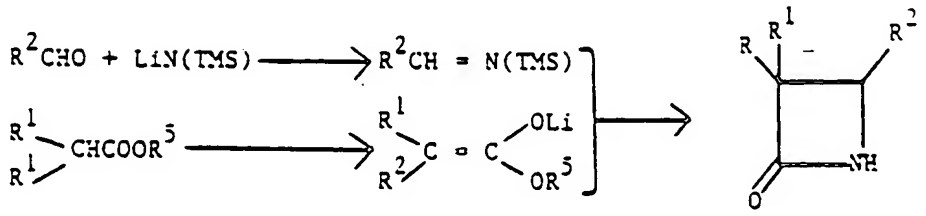
Scheme (e)

as taught by M. A. Krook and M. J. Miller (J. Org. Chem., 1988, 50, 1126-1128), the following type of compounds can be prepared.



Scheme (f)

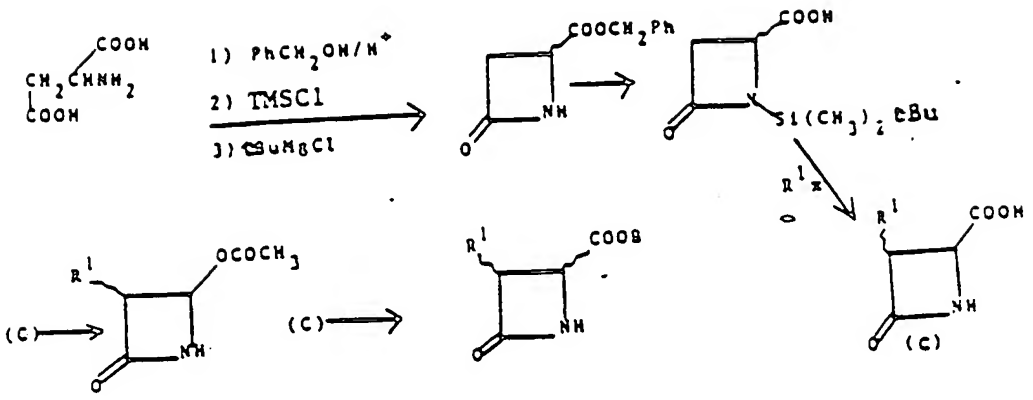
as taught by Hart, D. J. et al., (J. Org. Chem., 48, pp. 289-294, 1983); the following class of compounds can be prepared.



wherein R^5 is as previously defined; and
TMS is trimethylsilyl.

Scheme (g)

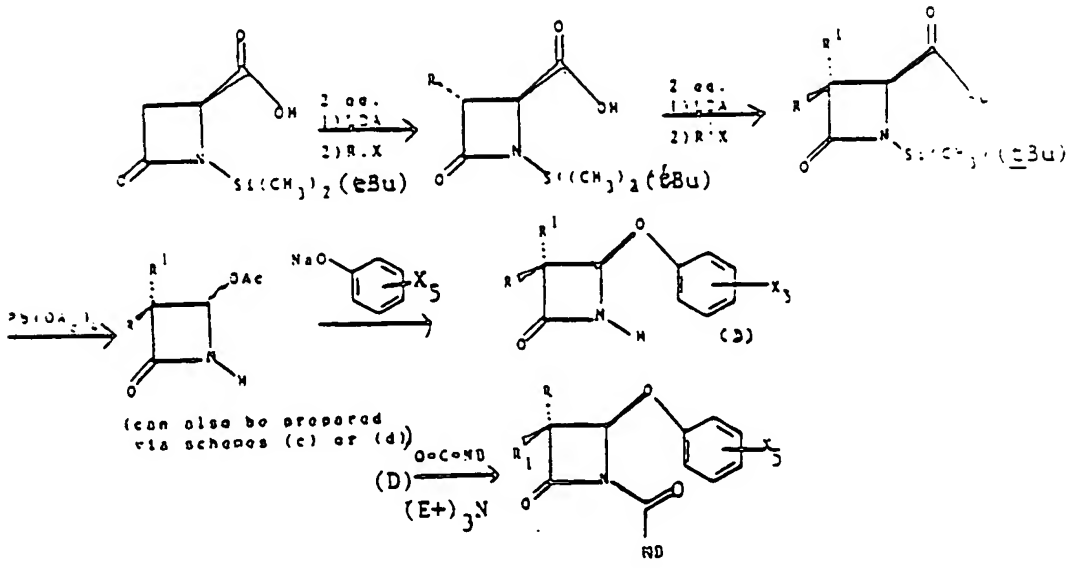
as taught by P. J. Reider and E. J. J. Grabowski (Tet. Lett., 23, p. 2293, 1982); the following groups of compounds can be prepared.



wherein R' is as previously defined.

Scheme (h)

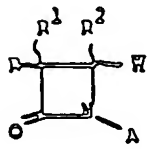
as illustrated by Examples 20 and 21:



This invention also relates to a method of treating inflammation in patients using a compound of Formula (I), particularly a preferred compound as the active constituent.

It has been found that the compounds of Formula (I) are effective inhibitors of the proteolytic function of human granulocyte elastase as shown below:

TABLE I



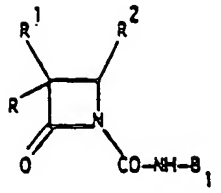
R	R^1	R^2	A	ID_{50} (μg/ml)	Ki (μM)	k_{obs}/I ($M^{-1}sec^{-1}$)
H	H	$SOCH_3$	$COCH_3$	10.00		
H	H	$OCOCH_3$	$COCH_3$	3.00		
H	C_2H_5	$OCOCH_3$	H	15.00		
H	C_2H_5	$OCOCH_3$	$COCH_3$	0.10	0.36	15100
H	n-propyl	$OCOCH_3$	$COCH_3$	0.01		
H	C_6H_5 (trans)	$COOC_2H_5$	H	10.00		
H	H	$COOCH_2C_6H_5$	$SO_2(p\text{-}C_6H_4\text{-}NO_2)$	3.00		
CH_3	CH_3	$OCOCH_3$	$COCH_3$	0.50		
H	C_6H_5 (trans)	$COOC_2H_5$	$SO_2(p\text{-}C_6H_4\text{-}NO_2)$	4.00		
H	C_6H_5 (cis)	$COOC_2H_5$	$SO_2(p\text{-}C_6H_4\text{-}NO_2)$	3.00		
H	CH_3O	$COOCH_2C_6H_5$	$COCH_3$	2.00		
H	n-propyl	$OCOCH_3$	$SO_3^-(Bu)_4N^+$	8.00		
H	C_2H_3 (cis)	$COOC_2H_5$	$SO_2(p\text{-}C_6H_4\text{-}NO_2)$	0.02		
H	C_2H_5 (cis)	$COOC_2H_5$	$SO_2(p\text{-}C_6H_4\text{-}NO_2)$	0.05		3925
H	C_2H_5 (trans)	$COOC_2H_5$	$SO_2(p\text{-}C_6H_4\text{-}NO_2)$	0.05		39300
H	C_2H_5 (trans)	$COOC_2H_5$	$SO_2(p\text{-}C_6H_4\text{-}CH_3)$	0.01		
H	n-propyl (trans)	$COOC_2H_5$	$SO_2(p\text{-}C_6H_4\text{-}NO_2)$	0.06		
H	CH_3CHCH (cis)	$COOC_2H_5$	$SO_2(p\text{-}C_6H_4\text{-}NO_2)$	0.05		
H	CH_2CH	$p\text{-}(C_6H_4\text{-}NO_2)$	H	1.50		
H	C_2H_5	$OCOCH_2CH_2COOH$	$COCH_3$		2.00	4514
H	C_2H_5 (trans)	OCOPh	$COCH_3$		0.19	91000

TABLE I (Continued)

R	R^1	R^2	A	ID_{50} (μg/ml)	Ki (μM)	k_{obs}/I (M^{-1} sec^{-1})
H	C_2H_5 (cis)	OCOPh	$COCH_3$		0.21	28500
H	C_2H_5	$OCOCH_3$	$COCH_2CH_2COOH$		1.43	2250
H	C_2H_5 (cis)	$OCOCH_3$	COPh		0.14	
H	C_2H_5 (trans)	$OCOCH_3$	COPh		0.34	76600
H	C_2H_5 (trans)	OPh	$COCH_3$		4.30	5270
H	C_2H_5 (trans)	OC_2H_5	$COCH_3$		11.90	1670
H	C_2H_5 (trans)	OPh-p-COOH	$COCH_3$		3.40	8727
H	C_2H_5 (trans)	OPh-p-COOH	$COOC_2H_5$		2.10	8680
H	C_2H_5 (trans)	OPh-p-COOH	$CONHCH_3$		16.50	
H	C_2H_5 (cis)	$CON(CH_2)_4$	$SO_2(p\text{-}C_6H_4\text{-}CH_3)$		27.70	541
H	C_2H_5 (cis)	$COOCH_2C_6H_4$-p-COOH	$SO_2(p\text{-}C_6H_4\text{-}CH_3)$		4.20	299
H	C_2H_5 (cis)	$CON(CH_3)CH_2COOH$	$SO_2(p\text{-}C_6H_4\text{-}CH_3)$		22.00	165
H	C_2H_5 (trans)	OCH_2COOH	$COOC_2H_5$		-	512
H	C_2H_5 (cis)	OCH_2COOH	$COOC_2H_5$		-	796
H	n-propyl (trans)	OCH_2COOH	$COOC_2H_5$		-	1504
H	C_2H_5 (trans)	$OCH_2CONHCH_2COOH$	$COOC_2H_5$		-	1000
H	C_2H_5 (trans)	$OCH(CH_3)COOH$	$COOC_2H_5$		-	346
H	C_2H_5 (cis)	$COOCH_2COOH$	$SO_2(P\text{-}C_6H_4\text{-}CH_3)$			1554

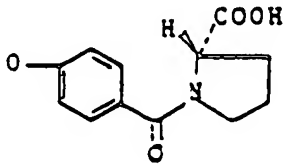
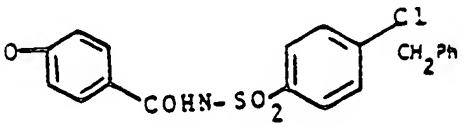
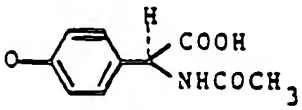
ID_{50} is the effective dosage in micrograms per milliliter (μg/ml) for 50% inhibition of the enzyme activity two minutes after time zero. Ki is the concentration of the inhibitor (micromolar, μM) giving 50% of the control enzyme activity. k_{obs}/I (M^{-1} sec^{-1}) is the second order rate constant of inactivation of the enzyme.

Table II



R	R^1	R^2	B_1	k_{obs} (l
C_3H_7	CH_3	O-(4-COOH-Ph)	CH_2Ph	1900
C_2H_5	CH_3	O-(4-COOH-Ph)	$CH(CH_3)Ph$	15.000
C_3H_7	H	O-(4-COOH-Ph)	CH_2Ph	5.000
C_2H_5	C_2H_5	O-(4-$CO(CH_2)_2$COOH-Ph)	CH_2(4-Ph-Ph)	107.045
C_2H_5	C_2H_5	O-(4-COOH-Ph)	CH_2(4-Ph-Ph)	37.000
C_2H_5	CH_2OCH_3	O-(4-COOH-Ph)	CH_2(4-Ph-Ph)	44.533
C_2H_5	C_2H_5	O-(4-NO_2-Ph)	CH_2Ph	6.847
C_2H_5	C_2H_5	O-(4-COOH-Ph)	CH_2 (2-Anthracene)	36.177
C_2H_5	C_2H_5	O-(2-CH_2CH-Ph)	CH_2Ph	2961
C_2H_5	C_2H_5	O-(4-CH_2COOH-Ph)	CH_2Ph	3175
C_2H_5	C_2H_5	O-(4-$CH_2CH(NH_3^+)CO_2^-$-Ph)	CH_2Ph	2540
C_2H_5	C_2H_5	O-(4-$NHCOCH_3$-Ph)	CH_2Ph	3503
C_2H_5	C_2H_5	O-(4-$NHCOCH_2CH_2$COOH-Ph)	CH_2Ph	2568
C_2H_5	C_2H_5	O-(4-CH_3CO-Ph)	CH_2-(4-COOH-Ph)	2807
C_2H_5	C_2H_5	O-(4-CH_3CO-Ph)	CH_2(4-CH_3CO-Ph)	5916
C_2H_5	C_2H_5	O-(4-COOH-Ph)	CH_2-(2-furyl)	5223
C_2H_5	C_2H_5	O-(4-COOH-Ph)	CH_2-(2-thienyl)	4925
C_2H_5	C_2H_5	O-(4-COOH-Ph)	$n-C_9H_{19}$	8300
C_2H_5	C_2H_5	O-(4-COOH-Ph)	$(CH_2)_3Ph$	4537
C_2H_5	C_2H_5	O-(4-COOH-Ph)	CH_2Naph	21.269

R	R^1	R^2	B_1	k 25℃ /1
C_2H_5	C_2H_5	O-(4-COOH-Ph)	$(CH_2)_4Ph$	10,894
C_2H_5	C_2H_5	O-Ph	CH_2-(4-COOH-Ph)	1501
C_2H_5	C_2H_5	O-(4-COOH-Ph)	CH_2-cyclohoxyl	1424
C_2H_5	H	O-(4-COOH-Ph)	CH_2Ph	4000
C_2H_5	CH_3	O-(4-COOH-Ph)	CH_2Ph	2000
$CH_2CH=CH_2$	H	O-(4-COOH-Ph)	CH_2Ph	5400
C_3H_7	C_2H_5	O-(4-COOH-Ph)	CH_2Ph	3230
cyclopentano (R and R^1 combinod and form tho cyclopontano ring)		O-(4-COOH-Ph)	CH_2Ph	1900
C_2H_5	CH_2OCH_3	O-(4-COOH-Ph)	CH_2Ph	1900
C_2H_5	CH_3	O-(4-COOH-Ph)	$CH_2CH(CH_3)Ph$	2553
C_2H_5	C_3H_7	O-(4-COOH-Ph)	CH_2-(2-Naph)	51,000
C_2H_5	C_2H_5	O-(4-COOH-Ph)	$CH(CH_3)$-(1-Naph)	14,128
C_2H_5	C_2H_5	O-(4-COOH-Ph)	CH_2-(4-Cl-Ph)	3419
C_2H_5	C_2H_5	O-(4-COOH-Ph)	$CH_2(4-CH_3-Ph)$	3965
C_2H_5	C_2H_5	O-(4-COOH-Ph)	$CH_2(4-F-Ph)$	2337
C_2H_5	C_2H_5	O-(4-COOH-Ph)	$CH_2(4-OCH_3-Ph)$	5162
C_2H_5	C_2H_5	O-(4-COOH-Ph)	$CH_2(4-NO_2-Ph)$	5075
C_2H_5	C_2H_5	O-(4-COOH-Ph)	$CH(CH_3)$-(3-Cl-4-cyclohoxyl-Ph)	20,776
C_2H_5	CH_2OCH_3	O-(4-COOH-Ph)	CH_2-(3,4-methylene-dioxy-Ph)	16,984
C_2H_5	C_2H_5	O-(4-COOH-Ph)	CH_2-(2-benzofuran)	13,151
C_2H_5	C_2H_5	O-(2-(6-COOH-Naph))	CH_2Ph	5561
C_2H_5	C_2H_5	O-(4-COOH-Ph)	CH_2(4-(4-Cl-Ph)-SO_2NHCO-Ph)	1730

R	R^1	R^2	B_1	k_{obs}/I
C_2H_5	C_2H_5	O-(3-CO-NHCH(COOH)-CH_2-Ph)	CH_2Ph	3047
C_2H_5	C_2H_5	O-(3-COOH-Ph)	CH_2Ph	1763
C_2H_5	C_2H_5	O-(4-COOH-Ph)	CH_2-(4-PhO-Ph)	12.036
C_2H_5	C_2H_5	O-(4-COOH-Ph)	CH_2-(4-$HN^+(CH_3)_2$-Ph) $^{\circ}CF_3COO^-$	9983
C_2H_5	C_2H_5	O-(4-COOH-Ph)	$(CH_2)_4OPh$	3447
C_2H_5	C_2H_5	O-(4-COOH-Ph)	$(CH_2)_4CH(CH)Ph$	4200
C_2H_5	C_2H_5	O-(4-$N^+(CH_3)_3I^-$-Ph)	CH_2Ph	1700
C_2H_5	C_2H_5	-1-imidazolyl	CH_2Ph	200
C_2H_5	C_2H_5		CH_2Ph	2000
C_2H_5	C_2H_5		CH_2Ph	5300
C_2H_5	C_2H_5		CH_2Ph	2422

Tablo II

(continuod)

R	R^1	R^2	R_1	k_{obs} /I
C_2H_5	H	O-(4-COOH-Ph)	Ph-4-COOH	13,563
C_3H_7	C_3H_7	O-(4-COOH-Ph)	CH_2Ph	2,500
allyl	C_2H_5	O-(4-COOH-Ph)	CH_2Ph°	1974
CH_2Ph	C_2H_5	O-(4-COOH-Ph)	CH_2Ph	87
C_2H_5	CH_2OCH_3	O-(4-COOH-Ph)	CH_2-2-Naph	50,000
C_2H_5	H	Ph-4-COOH	CH_2Ph	900
H	OMe	Ph-4-COOH	CH_2-2-Naph	1340
C_2H_5	C_3H_7	O-(4-COOH-Ph)	CH_2Ph-3-CF_3	55,000
C_2H_5	CH_3	O-(4-COOH-Ph)	CH(Et)-5-benzofuryl	750,000
C_2H_5	CH_3	O-(4-COOH-Ph)	CH(Et)-3-thienyl	78,800
C_2H_5	CH_2OCH_3	O-(4-COOH-Ph)	CH(nPr)Ph	75,000
C_2H_5	C_3H_7	O-(4-$CO(CH_2)_2COOH$-Ph)	CH(Et)Ph	87,000
C_2H_5	C_3H_7	O-(4-CH_2COOH-Ph)	CH(Et)Ph	54,000
C_2H_5	CH_3	O-(4-COOH-Ph)	Cyclopentyl	—
C_2H_5	CH_3	O-(4-COOH-Ph)	$CH(CH_3)CH_2CH_2CH_3$	—
C_2H_5	CH_3	O-(4-$CONH_2$Ph)	CH_2Ph	12,500
C_2H_5	CH_3	O-(4-COOH-Ph)	CH_2(3,5-diMe-4-COOH-Ph)	5,500
C_2H_5	CH_3	O-(4-$CONH_2$Ph)	CH_2(3,5-diMe-4-COOH-Ph)	30,000
C_2H_5	CH_3	O-(4-COOH-Ph)	CH_2(3,4-diMeO-Ph)	11,300

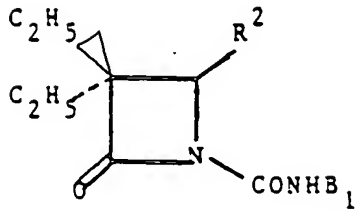
Me represents CH_3

Ph represents phanyl

Pr represents propyl

Bu represents butyl

Table III



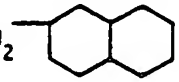
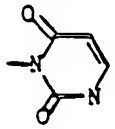
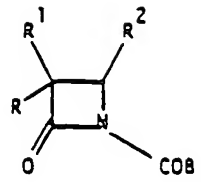
R^2	R^1	k_{obs}/I
OCH_2COOH	CH_2Ph-4-Ph	2901
O-(4-COOH-Ph)	CH_2 	4157
O-(allyl)	CH_2Ph-4-Ph	12,545
-1-imidazolyl	CH_2Ph-4-Ph	461
1-triazolyl	CH_2Ph-4-Ph	2144
(1-methyl-tetrazol-5-yl)thio	CH_2Ph	3658
(1-H-triazol-3-yl)thio	CH_2Ph	116
1-tetrazolyl	CH_2Ph	948
[2H-1-pyridonyl]	CH_2Ph	357
O-Ph-4-$CONH_2$	CH_2-2-Naph(6-COOH)	40,650
1-benzimidazolyl	CH_2Ph	69
	CH_2Ph	351
O-glycoryl	CH_2Ph	818
OCH_2CONH_2	CH_2-Ph-4-Ph	51,802
NH-COOHo	CH_2Ph	496
OCH_2-COOH	CH-(Et)-Ph	5711
OCH_2-$CONH_2$	CH-(Et)-Ph	102,974
O-(4-COOH-Ph)	nBu	—
O-(4-COOH-Ph)	cyclopentyl	—
O-$CH_2CON(Et)_2$	CH(Et)Ph	—

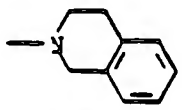
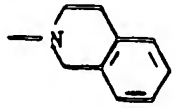
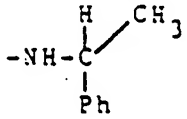
Table III

(Continued)

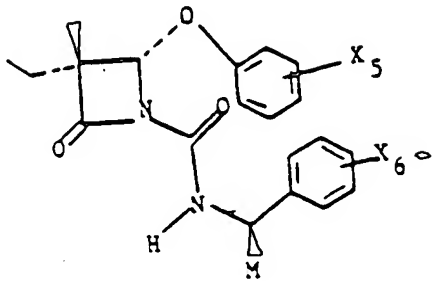
R^2	R_1	k_{obs}/I
O-(4-COOH-Ph)	CH_2Ph(2-OH)	1461
O-(4-COOH-Ph)	CH_2Ph(4-tBu)	21,774
O-(4-COOH-Ph)	CH_2Ph(4-(3-COOH)Ph)	14,727
O-(4-COOH-Ph)	CH_2Ph(4-CO-N⟨⟩O)	2036
O-(4-COOH-Ph)	CH_2Ph(4-CH_2Ph)	8032
O-(4-COOH-Ph)	CH_2Ph(3-CH_3)	6932
O-(4-COOH-Ph)	CH_2Ph(3,4-$(CH_2)_4$)	62,883
O-(4-COOH-Ph)	CH_2Ph(3,4-DiMe)	20,600
O-(4-COOH-Ph)	CH_2Ph(4-i-Pr)	18,846
O-(4-COOH-Ph	CH_2Ph(4-$S(O)_2Me$)	3350
O-(4-COOH-Ph)	CH_2Ph(4-COMe)	5916
O-(4-COOH-Ph)	CH_2Ph(4-OMe-3-Me)	13,126
O-(4-COOH-Ph)	CH_2-Ph(4-OCH_2Ph)	12,036
O-(4-CH(COOH)NHAc-Ph)	CH_2Ph	1675
O-(4-CH(OH)COOH-Ph)	CH_2Ph(3,4-DiMe)	17,626
O-(3-OH-4-COOH-Ph)	CH_2Ph(4-Me)	9252
O-(2-$(CH_2)_3NMe_2$-Ph)	CH_2Ph	629
O-(4-CH_2COOH-Ph)	CH_2Ph(4-Ph)	28,870

Tablo IV



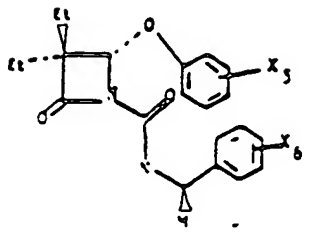
R	R^1	R^2	B	k_{obs}/I
C_2H_5	$-CH_3$	O-(4-COOH-Ph)		4376
C_2H_5	-H	O-(4-COOH-Ph)		10.066
C_3H_7	C_3H_7	O-(4-COOH-Ph)		1446 (lower ref.) 4324 (higher ref.)
C_2H_5	H	O-(4-COOH-Ph)	$-N(CH_2Ph)_2$	5977
C_2H_5	H	O-(4-COOH-Ph)	$-OCH_2-(4-COOC_2H_5-Ph)$	227.460
C_2H_5	C_2H_5	O-(4-COOH-Ph)	$-OCH_2-(4-COOC_2H_5-Ph)$	14.331
C_2H_5	H	O-(4-COOH-Ph)	$-N(C_2H_5)(CH_2Ph)$	82.956

Tablo V



X_5	R	X_6	k_{obs}/I
4-COOH	Et	H	92.000
4-COOH	nPr	H	152.000
4-COOH	CH_2OMe	H	6.094
4-CH_2COOH	Et	H	140.000
4-COOH	Me	4-Me	47.000
4-COOH	Et	4-Me	—
4-COOH	$PhCH_2$	H	25.000
4-CH_2COOH	nPr	H	227.000
4-COOH	nPr	CH_3	—
4-COOH	nPr	H	120.000
4-COOH	Et	3,4-(OCH_2O)	—
4-CH_2COOH	nBu	H	—
4-COOH	allyl	H	—

Tablo VI



X_5	H	X_6	k_{obs}/I
4-COOH	Me	H	4016
4-COOH	Me	4-Ph	74,000
4-CH_2COOH	Me	H	8,373
4-COOH	Me(s)	4-Ph	49246
4-COOH	Ph	Ph	67754
4-COOH	Me	4-(2'-Cl-Ph)	245130
4-COOH	Et	4-Ph	26382
4-COOH	Et	H	76204
4-CO-$(CH_2)_2$-COOH	Me	H	37084
4-CO-$(CH_2)_2$COCH	Et	H	272190
4-COOH	nPr	H	116060
3,5-Me_2-4-COOH	Et	H	24,994
4-CH_2COOH	Et	H	126,000
3-OH-4-COOH	Et	H	124560
3-CH_2COOH	Me	H	5885
4-CH=CH-COOH	Me	H	9101
4-COOH	CH_2OMe(S)	H	6981
4-CH_2COOH	CH_2OMe(S)	H	
4-COOH	Me	-Me	10680
4-COOH	iPr(S)	H	4743
4-COOH	iPr	H	177075
4-CH_2COOH	nPr	H	188,000
4-CH_2COOH	CH_2OMe(R)	H	11004
3,5-Me_2-4-COOH	nPr	H	

Table VI

(Continued)

X_5	R	X_6	k_{obs}/I
3-CH_2COOH	Et	4-Me	
4-$(CH_2)_2COOH$	Me	H	9481
3-CH_2COOH	Et	H	81018
4-COOH	CH_2OMe(R)	H	6981
4-COOH	Et	3-Me	
4-CH_2COOH	Et	3-Me	
4-$CO(CH_2)_2COOH$	allyl	4-Me	
4-COOH	Me	4-Me	
4-CH_2COOH	Et	3-Cl	
4-COOH	Et	3-Cl	
4-COOH	allyl	3-Me	
4-COOH	nPr	3-Me	
4-CH_2COOH	allyl	4-Me	664,000
3-CH_2COOH	allyl	4-Me	
4-CH_2COOH	allyl	3-Me	
4-CH_2COOH	nPr	3-Me	
4-$CO(CH_2)_2COOH$	nPr	4-Me	
3-CH_2COOH	allyl	H	
3-CH_2COOH	CH_2OMe(S)	H	
4-COOH	allyl	H	
4-CH_2COOH	allyl	H	
4-COOH	Et	4-Me	
4-COOH	Et(S)	4-Me	
4-COOH	allyl	4-Me	
4-COOH	nPr	4-Me	389,000
3-CH_2COOH	nPr	4-Me	
4-CH_2COOH	nPr	4-Me	557,000

Table VI

(Continued)

X_5	R	X_6	i_{obs}/I
3-CH_2COOH	Et	4-Cl	
4-COOH	Et	4-Cl	
4-CH_2COOH	Et	4-Me	
3-CH_2COOH	Et	3-Cl	
4-COOH	allyl	3,4-methylenedioxy	
4-COOH	nPr	3,4-methylenedioxy	
4-CH_2COOH	allyl	3,4-methylenedioxy	605.000
4-CH_2COOH	nPr	3,4-methylenedioxy	867.000
3-CH_2COOH	CH_2COOH	4-Me	
3-CH_2COOH	nPr	H	
4-COOH	Et	3,4-methylenedioxy	
4-CH_2COOH	Et	3,4-methylenedioxy	
4-COOH	Et	3,4-Me_2	
4-COOH	$CH_2C\equiv CCH_3$	H	
4-CH_2COOH	$CH_2C\equiv CCH_3$	H	
4-COOH	nBu	H	
2-NO_2-4-CH_2COOH	Et	H	
4-COOH	Et	4-F	
4-COOH	Et	3-Me-4-OMe	

Protocol - Enzyme Assays for the Inhibition of Human Polymorphonuclear Leukocyte Elastase Via Hydrolysis of N-t-Boc-alanyl-alanyl-prolylalanine-p-nitroanilide (Boc-AAPAN) or N-t-Boc-alanyl-prolylvaline-p-nitroanilide (Boc-AAPVN) Reagent:

0.05M TES (N-tris[hydroxymethyl]methyl-2-amino-ethanesulfonic acid) Buffer, pH 7.5.

0.2 mM Boc-AAPAN or Boc-AAPVN.

To prepare substrate, the solid was first dissolved in 10.0 ml DMSO. Buffer at pH 7.5 was then added to a final volume of 100 ml.

Crude extract of human polymorphonuclear leukocytes (PMN) containing elastase activity.

Inhibitors (azetidinones) to be tested dissolved in DMSO just before use.

Assay Procedure:

To 1.0 ml of 0.2 mM Boc-AAPAN in a cuvette, 0.01-0.1 ml of DMSO with or without inhibitor was added. After mixing, a measurement was tak n at 410 mu to detect any spontaneous hydrolysis due to presence of test compound. 0.05 Milliliters of PMN extract was then added and the ΔOD/min at 410 mu was measured and recorded. Beckman model 35 spectrophotometer was used.

Results:

Results in Table I were reported as ID_{50}. ffective dosage in micrograms per milliliter (μg/ml) for 50% inhibition of the enzyme activity 2 minutes after zero time.

Results were also express d as Ki, the micromolar concentration of the inhibitor (μM) giving 50% of the control enzyme activity; or as $k_{obs/I}$ which is the second order rate constant in per mole per s cond for inactivation of the enzyme.

Comments:

The elastase activity in the crude PMN extract may vary from one preparation to another. A control of each new batch is run, and the volume added in the assay procedure is adjusted according to activity.

Accordingly, the compounds of Formula (I) can be used to reduce inflammation and relieve pain in diseases such as emphysema, rheumatoid arthritis, osteoarthritis, gout, bronchial inflammation, atherosclerosis, sepsis, septicemia, shock, periodontitis, cystic fibrosis, infectious arthritis, rheumatic fev r and the like.

For treatment of inflammation, fever or pain, the compounds of Formula (I) may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used h rein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, dogs, cats, etc., the compounds of the invention are effective in the treatment of humans.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweet ning agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparation. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium st arate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for exampl peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for th manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadeca-ethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate. The said aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sw tening agents, such as sucrose or saccharin.

Oily susp nsion may be formulated by susp nding the activ ingredi nt in a veg table oil, for example arachis oil, olive oil, sesam oil or coconut oil, or in a mineral oil such as liquid paraffin. Th oily suspensions may contain a thick ning agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening ag nts such as those set forth above, and flavoring agents may be added to provide a palatabl

oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and on or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweet ning, flavoring .and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oils, or ℞ mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of Formula (I) may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the anti-inflammatory agents are employed.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 5 mg to 5 gm of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain betw en from about 25 mg to about 500 mg of active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and th severity of the particular disease undergoing therapy.

EXAMPLE 1

1-p-nitrophenylsulfonyl-4-benzyloxycarbonyl azetidin-2-one

Diazabicycloundecane (152 mg, 1 mM) was added to a mixture of 205 mg (1 mM) 4-benzyloxycarbonyl azetidin-2-one and 181 mg (1 mM) p-nitrobenzenesulfonyl chloride in 10 ml methylene chloride at room temperature. After stirring 2-1/2 hours, the orange solution was washed with water, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel in hexane/ethyl acetate to yield 64 mg (17%) of 1-p-nitrophenylsulfonyl-4-b nzyloxycarbonyl azetidin-2-one.

NMR ($CDCl_3$): δ 3.3 (2H, doublet-quartet), 4.8 (qt. 1H), 5.2 (s, 2H), 7.2 (s, 5H), 8.2 (mlt. 4H).

EXAMPLE 2

1-Acetyl-3,3-dimethyl-4-acetoxyazetidin-2-one

Step A: Preparation of 2-methyl-prop-1-enylacetate

A mixture of 72 g (1 M) isobutyraldehyde, 153 g (1.5 M) acetic anhydride and 12 g (0.125 M) potassium acetate was refluxed seven hours. The cooled reaction mixture was washed with water and stirred with 300 ml saturated $NaHCO_3$ at 0° C for 45 minutes. The organic phase was dried over K_2CO_3 to yield a yellow oil which was distilled at atmospheric pressure to give 35.41 g (31%) of 2-methyl-prop-1-enylacetate, b.p. 122-126°.
NMR ($CDCl_3$): δ 1.6 (s, 6H), 2.1 (s, 3H), 6.9 (mlt, 1H).

Step B: Preparation of 3-3-dimethyl-4-acetoxyazetidin-2-one

Chlorosulfonyl isocyanate (16 ml) was added to a solution of 22.8 g (0.2 M) 2-methyl prop-1-enyl acetate in 50 ml methylene chloride at 0° under nitrogen. After stirring at 0° for 20 hours, the reaction mixture was added to a mixture of 20 ml water, 90 g ice, 48 g $NaHCO_3$ and 16.6 g Na_2SO_3 and stirred at 0° for 30 minutes. This was then extracted with 300 ml CH_2Cl_2 and the organic phase washed with brine, dried over $MgSO_4$ and concentrated in vacuo to give 27.75 g oil which was chromatographed on silica gel in hexane/ethyl acetate to yield 2.17 g (8.5%) of 3,3-dimethyl-4-acetoxyazetidin-2-one.
NMR ($CDCl_3$): δ 1.2 (s, 3H), 1.3 (s, 3H), 2.2 (s, 3H), 5.6 (s, 1H).

Step C: Preparation of 1-acetyl-3,3-dimethyl-4-acetoxyazetidin-2-one

A mixture of 283.3 mg (1.8 mM) 3,3-dimethyl-4-acetoxyazetidin-2-one, 2 ml pyridine and 2 ml acetic anhydride was heated to 100° in a sealed tube for 36 hours. The reaction mixture was concentrated in vacuo and the residue chromatographed on silica gel in hexane:ethyl acetate to yield 295 mg (82%) of 1-acetyl-3,3-dimethyl-4-acetoxyazetidin-2-one.
NMR ($CDCl_3$): δ 1.2 (s, 3H), 22 (s, 3H), 2.5 (s, 3H), 6.1 (s, 1H).

EXAMPLE 3

1-Acetyl-4-acetoxy-3-n-propylazitidin-2-one

Step A: Preparation of Pent-1-enyl acetate

A mixture of 86 g (1M) valeraldehyde, 153 g (1.5 M) acetic anhydride, and 12 g (0.125 M) potassium acetate, was refluxed for 8 hours. The cooled mixture was then stirred with 100 ml saturated aqueous $NaHCO_3$ for one hour. The organic phase is separated, dried over K_2CO_3, and distilled at 40 mm to yield 46.15 g (45%) of pent-1-enylacetate, b.p. 89° C.
NMR ($CDCl_3$): δ 1.0 (tr, 3H), 1.2-2.0 (mlt., 4H), 2.1 (s, 3H), 4.7-5.6 (mlt, 1H), 7.0-7.3 (mlt., 1H).

Step B: Preparation of 4-acetoxy-3-n-propylazetidin-2-one

Eight hundred microlitrs of chlorosulfonyl isocyanate was added to a solution of 1.28 g (10 mM) pent-1-enyl acetate in 5 ml methylene chloride at 0° under nitrogen. After stirring at 0° 5 days, the reaction mixture was added dropwise to a mixture of 5 g ice, 1.15 ml water, 2.82 g $NaHCO_3$ and 1.0 g Na_2SO_3 and stirred at 0° for 30 minutes. The mixture was extracted with 2 X 25 ml methylene choride and the

combined organic phases washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel in hexane/ethyl acetate to yield 60 mg trans 4-acetoxy-3-n-propylazetidin-2-one (3.4%).
NMR ($CDCl_3$): δ 1.0 (mlt., 3H), 1.7 (mlt., 4H), 2.2 (s, 3H), 3.2 (tr, 1H), 5.6 (s, 1H), 6.7 (lrs, 1H).

Step C: Preparation of 1-acetyl-4-acetoxy-3-n-propylazeticin-2-one

A mixture of 56 mg (0.33 mM) 4-acetoxy-3-propylazetidin-2-one, 1 ml acetic anhydride and 1 ml pyridine was stirred at 100° in a sealed tube for 24 hours. After concentrating in vacuo the residue was chromatographed on silica gel in hexane/ethyl acetate, to yield 16 mg (23%) 1-acetyl-4-acetoxy-3-n-propylazetidine-2-one.
NMR ($CDCl_3$): δ 1.0 (br tr, 3H), 1.7 (mlt., 4H), 2.2 (s, 3H), 2.4 (s, 3H), 3.2 (tr, 1H), 6.1 (d, 1H).

EXAMPLE 4

1-Acetyl-4-methylsulfonylazetidin-2-one

Step A: Preparation of 1-acetyl-4-methylthioazetidin-2-one

A mixture of 300 mg (2.6 mM) 4-methylthioazetidin-2-one, 10 ml acetic anhydride and 10 ml pyridine was stirred at 100° in a sealed tube 24 hours. After concentrating in vacuo, the residue was chromatographed on silica gel in hexane/ethyl acetate to yield 324 mg (78%) of 1-acetyl-4-methylthioazetidine-2-one.
NMR ($CDCl_3$): δ 2.4 (s, 3H), 2.41 (s, 3H), 3.2 (doublet-quartet, 2H), 5.1 (doublet-doublet, 1H).

Step B: Preparation of N-acetyl-4-methylsulfinylazetidin-2-one

A mixture of 130 mg (0.82 mM) N-acetyl-4-methylthioazetidinone and 200 mg (0.93 nM) 80% m-chloroperbenzoic acid in 5 ml methylene chloride was stirred at room temperature 5 minutes. After removing the solvent in vacuo. The residue was chromatographed on 2-2000 μ-silica gel plates in hexane/ethyl acetate to yield 57 mg (40%) of 1-acetyl-4-methylsulfinylazetidine-2-one.
NMR ($CDCl_3$): δ 2.4 (s, 3H), 2.6 (s, 3H), 3.5 (mlt., 2H), 4.9 (mlt., 1H).

EXAMPLE 5

3-Azido-4-carboethoxy-1-(p-methoxyphenyl)azetidin-2-one

To a solution of 3.06 g of azidoacetyl chloride in 50 ml of CH_2Cl_2 was added dropwise a solution of 3.57 ml of triethylamine and 5.3 g of the imine formed from ethylglyoxalate and p-anisidine in 50 ml CH_2Cl_2, with cooling at such a rate that the reaction temperature remained below 5°. The reaction was then stirred at room temperature for three hours and then washed sequentially with 1N HCl, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride. The organic phase was dried over magnesium sulfate, filtered, and evaporated, and the crude residue was recrystallized from carbon tetrachloride-hexane to afford 3.7 g. of 3-azido-4-carboethoxy-1-(p-methoxyphenyl)azetidine-2-one; m.p. 80-85°.
NMR ($CDCl_3$): δ 7.2 (d, J = 9, 2H), 6.75 (d, J = 9, 2H), 4.9 (d, J = 6, 1H), 4.6 (d, J = 6, 1H), 4.25 (q, J = 8, 2H), 3.7 (s, 3H), 1.25 (t, J = 8, 3H).

EXAMPLE 6

4-Carboethoxy-3-chloro-1-(p-methoxyphenyl)azetidine-2-one

4-carboethoxy-3-chloro-1-(p-methoxyphenyl)azetidine-2-one was prepared by following th same procedure as described in Example 5 but using chloroacetyl chloride and the imine formed from ethylglyoxalate and p-anisidine as the starting material. The crude product was recrystallized from ether (h xane) to give 3.1 g of 4-carboethoxy-3-chloro-1-(p-methoxyphenyl)azetidine-2-one, m.p. 99-100°.
NMR ($CDCl_3$): δ 7.2 (d, J = 9, 2H), 6.8 (d, J = 9, 2H), 5.1 (d, J = 6, 1H), 4.7 (d, J = 6, 1H), 4.25 (q, J = 7, 2H), 3.7 (s, 3H), 1.25 (t, J = 7, 3H).

EXAMPLE 7

4-Carboethoxy-3-methoxy-1-(p-methoxyphenyl)azetidine-2-one

4-Carboethoxy-3-methoxy-1-(p-methoxyphenyl)azetidine-2-one was prepared by following the same procedure as described in Example 5 but using methoxyacetyl chloride as the starting material. After chromatography the compound crystallized as a white solid: m.p. 116-118°.
NMR ($CDCl_3$): δ 7.2 (d, J = 9, 2H), 6.75 (d, J = 9, 2H), 4.7 (d, J = 5, 1H), 4.6 (d, J = 5, 1H), 4.2 (q, J = 5, 2H), 3.7 (s, 3H), 3.5 (s, 3H), 1.2 (t, J = 5, 3H).

EXAMPLE 8

4-Carboethoxy-1-(p-methoxyphenyl)-3-phenylazetidin-2-one

To a solution of 17 ml of triethylamine and 5.0 g of the imine formed from ethyl glyoxalate and p-anisidine in 100 ml of refluxing 1,2-dichloroethane was added dropwise over 2 hours a solution of 16 ml of freshly distilled phenylacetyl chloride in 50 ml of dichloroethane. After refluxing for three hours the reaction was worked-up as per the 3-azidoazetidinone. The crude residue was chromatographed to yield the cis and trans isomers of 4-carboethoxy-1-(p-methoxyphenyl)-3-phenylazetidin-2-one as oils: cis: NMR ($CDCl_3$): δ 7.2 (m, 7H), 6.7 (d, J = 9, 2H), 4.7 (s, 2H), 3.6 (s, 3H), 3.6 (q, J = 7, 2H), 0.7 (t, J = 7, 3H); trans: NMR ($CDCl_3$): δ 7.3 (m, 7H), 6.8 (d, J = 9, 2H), 4.5 (d, J = 2, 1H), 4.45 (d, J = 2, 1H), 4.1 (q, J = 7, 2H), 3.6 (s, 3H), 1.2 (t, J = 7, 3H).

EXAMPLE 9

4-Carboethoxy-1-(p-methoxyphenyl)-3-vinylazetidin-2-one

4-Carboethoxy-1-(p-methoxyphenyl)-3-vinylazetidine-2-one was prepared by following the same procedure as described in Example 8 but using crotonyl chloride as the reagent. After chromatography the cis and trans isomers of the compound were obtained: cis (m.p. 70-72°), NMR ($CDCl_3$): δ 7.2 (d, J = 9, 2H), 6.8 (d, J = 9, 2H), 5.2-5.8 (m, 3H), 4.6 (d, J = 6, 1H), 4.2 (m, 3H), 3.7 (s, 3H), 1.2 (t, J = 7, 3H); trans (oil), NMR ($CDCl_3$): δ 7.25 (d, J = 9, 2H), 6.8 (d, J = 9, 2H), 5.7-6.2 (m, 1H), 5.2-5.5 (m, 2H), 4.25 (br.s., 1H), 4.2 (q, J = 7, 2H), 3.9 (dd, J = 1, Jz = 6, 1H), 3.75 (s, 1H), 1.25 (t, J = 7, 3H).

EXAMPLE 10

4-Carboethoxy-3-ethyl-1-(p-m thoxyphenyl)azetidin-2-one

The cis and trans isomers of 4-carboethoxy-3-vinyl-1-(p-m thoxyphenyl)azetidine-2-on are each hydrogenated with palladium on carbon in ethanol to yield the corresponding cis and trans isomers of 4-carboethoxy-3-ethyl-1-(p-methoxy-phenyl)azetidine-2-one.

EXAMPLE 11

4-Carboethoxy-1-(p-methoxyphenyl)-3-(N-methyl-trifluoroacetamido)azetidin-2-one

A solution of 2.16 g of 3-azido-4-carboethoxy-1-(p-methoxyphenyl)-azetidine-2-one in ethanol was hydrogenated with palladium to yield 4-carboethoxy-1-(p-methoxyphenyl)-3-aminoazetidin-2-one. This amine was acylated with 1.1 ml of trifluoro acetic anhydride in 10 ml CH_2Cl_2 containing 1.5 ml pyridine, followed by methylation using 1 ml dimethyl sulfate in 30 ml acetone containing 3 g potassium carbonate. After isolation, the crude product was crystallized to give 2.2 g of 4-carboethoxy-1-(p-methoxyphenyl)-3-(N-methyltrifluoroacetamido)azetidine-2-one, m.p. 102-104°.
NMR ($CDCl_3$): δ 7.2 (d, J = 9, 2H), 6.75 (d, J = 9, 2H), 5.5 (d, J = 6, 1H), 4.7 (d, J = 6, 1H), 4.2 (q, J = 7, 2H), 3.7 (s, 3H), 3.2 (br.s., 3H), 1.2 (t, J = 7, 3H).

EXAMPLE 12

4-Carboethoxy-3-methoxyazetidin-2-one

To a solution of 1.4 g of 4-carboethoxy-3-methoxy-1-(p-methoxyphenyl)azetidine-2-one in 50 ml acetonitrile at 0° was added a solution of 8.23 g of cerric ammonium nitrate in 50 ml H_2O over 3 minutes. After stirring at 0° for 1 hour the solution was poured into 200 ml of 10% sodium sulfite and extracted with 3 X 75 ml of ethyl acetate. The combined organic extracts were washed with 10% sodium sulfite and saturated sodium chloride solutions and dried over sodium sulfate. Filtration and evaporation gave an amber oil which was recrystallized from methylene chloride:hexane to give 700 mg of 4-carboethoxy-3-methoxyazetidine-2-one; m.p. 91-92°.
NMR ($CDCl_3$): δ 7.1 (br.s, 1H), 4.7 (dd, J_1 = 2, J_2 = 5, 1H), 4.3 (d, J = 5, 1H), 4.15 (q, J = 7, 2H), 3.4 (s, 3H), 1.25 (t, J = 7, 3H).

Following substantially the same procedure as described in Example 12 but using an appropriate 3-substituted azetidinone compounds (a) - (f) were prepared:

(a) 4-Carboethoxy-3-chloroazetidin-2-one
NMR ($CDCl_3$): δ 7.3 (br.s., 1H), 5.0 (dd, J_1 = 2, J_2 = 6, 1H), 4.4 (d, J = 6, 1H), 4.2 (q, J = 7, 2H), 1.3 (t, J = 7, 3H).

(b) 4-Carboethoxy-3-phenylazetidin-2-one-2-(cis and trans)
NMR ($CDCl_3$): cis: δ 7.2 (s, 5H), 6.4 (br.s., 1H), 4.7 (d, J = 6, 1H), 4.4 (d, J = 6, 1H), 3.7 (q, J = 7, 2H), 0.75 (t, J = 7, 3H); trans δ 7.2 (s, 5H), 6.9 (br.s, 1H), 4.3 (br.d, J = 2, 1H), 4.1 (q, J = 7, 2H), 4.0 (d, J = 2, 1H), 1.2 (t, J = 7, 3H).

(c) 4-Carboethoxy-3-(N-methyltrifluoroacetamido) azetidin-2-one
NMR ($CDCl_3$): δ 7.2 (br.s., 1H), 5.4 (d, J = 6, 1H), 4.5 (d, J = 6, 1H), 4.15 (q, J = 7, 2H), 3.2 (s, 3H), 1.2 (t, J = 7, 3H).

(d) 4-Carboethoxy-3-vinylazetidin-2-one(cis and trans)
NMR ($CDCl_3$) cis: δ 7.1 (br.s., 1H), 5.2-5.8 (m, 3H), 4.0-4.4 (m, 4H), 1.25 (t, J = 7, 3H); trans: δ 7.25 (br.s., 1H), 5.0-6.2 (m, 3H), 4.1 (q, J = 7, 2H), 3.9 (d, J = 2, 1H), 3.7 (dd, J_1 = 2, J_2 = 7, 1H), 1.2 (t, J = 7, 3H).

(e) 4-Carboethoxy-3-ethylazetidin-2-one
Cis: NMR($CDCl_3$): δ 6.9 (br. s., 1H); 4.2 (m, 3H); 3.4 (dd, J_1 = 6, J_2 = 8, 1H); 1.51 (q, J = 8, 2H); 1.2 (t, J = 7, 3H); 1.0 (t, J = 8, 3H).
Trans: NMR($CDCl_3$): δ 6.8 (br. s., 1H); 4.2 (q, J = 7, 2H); 3.8 (d, J = 2, 1H); 3.2 (dd, J_1 = 2, J_2 = 7, 1H); 1.8 (-(dq, J_1 = 2, J_2 = 8, 2H); 1.2 (t, J = 7, 3H); 1.0 (t, J = 8, 3H).

(f) 3-Azido-4-carboethoxyazetidin-2-one

EXAMPLE 13

4-Carboethoxy-3-(N-methyltrifluoroacetamido)azetidine-2-one-1-sulfonic acid tetrabutylammonium salt

To a solution of 140 mg of 4-carboethoxy-3-(N-methyltrifluoroacetamido)azetidine-2-one in 5 ml of pyridine at 80° was added 250 mg of sulfur trioxide pyridine complex, and the resulting mixture was stirred for 30 minutes at 80°. The solution was poured into 100 ml of 0.5 N KH_2PO_4 and extracted with 2 X 25 ml of methylene chloride. The combined organic washes were back-extracted with 25 ml of KH_2PO_4 solution. The combined aqueous phases were then treated with 680 mg of tetrabutylammonium hycrogen sulfate and extracted with 3 X 50 ml of methylene chloride. After drying (sodium sulfate) and evaporation of the organic phase the crude 4-carboethoxy-3-(N-methyltrifluoroacetamido)azetidine-2-one-1-sulfonic acid tetrabutylammonium salt was chromatographed to yield an oil.

NMR ($CDCl_3$): δ 5.3 (d, J = 6, 1H), 4.7 (d, J = 6, 1H), 4.15 (q, J = 7, 2H), 3.2 (m, 11H), 0.8-1.8 (m, 31H).

Applying the same procedure as described above, the following tetrabutylammonium salts of other azetidine derivatives were prepared:

(a) 4-Carboethoxy-3-methoxyazetidin-2-one-1-sulfonic acid tetrabutylammonium salt

NMR ($CDCl_3$): δ 4.55 (d, J = 6, 1H), 4.5 (d, J = 6), 1H), 4.1 (q, J = 7, 2H), 3.4 (s, 3H), 3.2 (m, 8H), 0.8-1.8 (m, 31H).

(b) 4-Carboethoxy-3-vinylazetidin-2-one-1-sulfonic acid tetrabutylammonium salt

EXAMPLE 14

4-Carboethoxy-1-(p-nitrobenzenesulfonyl)-3-phenylazetidin-2-one

To a solution of 720 mg of 4-carboethoxy-3-trans-phenylazetidin-2-one in 20 ml methylene chloride at 0° were added sequentially 595 mg of p-nitrobenzenesulfonyl chloride and 0.48 ml of DBU. The solution was stirred for several hours, diluted with 50 ml of methylene chloride, washed once with water and dried over sodium sulfate. Filtration and evaporation gave a crude residue which was chromatographed to yield pure 4-carboethoxy-1-(p-nitrobenzenesulfonyl)-3-phenyl-azetidin-2-one.

NMR ($CDCl_3$): δ 8.3 (d, J = 9, 2H), 8.2 (d, J = 9, 2H), 7.2 (br.s., 5H), 4.0 (q, J = 7, 2H), 3.7 (m, 2H), 1.2 (t, J = 7, 3H). Similarly prepared was the corresponding cis-3-phenyl compound. NMR ($CDCl_3$): δ 8.4 (d, J = 9, 2H), 8.25 (d, J = 9, 2H), 7.2 (s, 5H), 5.0 (s, 1H), 3.7 (m, 3H), 0.85 (t, 5 = 7, 3H).

Following the same procedure as described above but using appropriate reagents the following compounds were prepared:

(a) 4-Carboethoxy-1-(p-nitrobenzensulfonyl)-3-vinylazetidin-2-one

NMR ($CDCl_3$): cis: δ 8.3 (d, J = 9, 2H), 8.2 (d, J = 9, 2H), 5.2-6.0 (m, 3H), 4.0-4.6 (m, 4H), 1.2 (t, J = 7, 3H); trans: δ 8.2 (d, J = 9, 2H), 8.15 (d, J = 9, 2H), 5.2-6.0 (m, 3H), 3.9-4.4 (m, 4H), 1.25 (t, J = 7, 3H)

(b) 4-Carboethoxy-3-ethyl-1-(p-nitrobenzenesulfonyl)azetidin-2-one

(c) 3-Azido-4-carboethoxy-1-(p-nitrobenzenesulfonyl) azetidin-2-one

(d) 4-Carboethoxy-3-chloro-1-(p-nitrobenzensulfonyl)azetidin-2-one

EXAMPLE 15

4-Carboethoxy-3-phenyl-1-trifluorom thanesulfenylaz tidin-2-one

To a mixtur of 1.2 g of 4-carboethoxy-3-phenylazetidin-2-one and 1.2 ml of triethylamin in 25 ml of methylene chloride at 0° was added dropwise over 10 minutes 11.25 ml of a 10% solution of trifluoromethan sulfenyl chloride in ether. After stirring for several hours the solution was washed with water, dried over sodium sulfate, filtered and evaporated. The crude residue was chromatographed to yield pure 4-carboethoxy-3-phenyl-1-trifluoromethanesulfenylazetidin-2-one as an oil.
NMR ($CDCl_3$): δ 7.2 (s, 5H), 4.6 (d, J = 3, 1H), 4.3 (m, 3H), 1.3 (t, J = 7, 3H).

EXAMPLE 16

1-Tosyloxymethyl-3-n-Propyl-4-p-nitrophenylthioazetidin-2-one

Step A: Preparation of 3-Propyl-4-p-nitrophenylthio azetidin-2-one

3-Propyl-4-acetoxy azetidinone, 171 mg, is refluxed with 200 mg p-nitrophenyl thiol in 10 ml benzene for 6 hours. The solution is washed 3x with aqueous Na_2CO_3, dried with $MgSO_4$, filtered and evaporated. The residue is chromatographed on silica gel, eluting with 10:1 $CHCl_3$-EtOAc, affording 3-Propyl-4-p-nitrophenylthioazetidin-2-one.

Step B: Preparation of 1-Tosyloxymethyl-3-n-propyl-4-p-nitrophenylthio azetidin-2-one

3-Propyl-4-p-nitrophenylthioazetidine-2-one, 266 mg, is stirred overnight at room temperature with 0.25 ml aqueous formalin (37%) and 17 mg K_2CO_3. Water and formaldehyde are removed in vacuo, and flushed with 2 ml pyridine. The residue is taken up in 4 ml pyridine and treated for 1 hour at room temperatur with 200 mg p-toluenesulfonyl chloride. The pyridine is evaporated and replaced with 5 ml benzene. The solution is washed with aqueous H_3PO_4 and then aqueous K_2HPO_4, dried with $MgSO_4$, filtered and evaporated. The residue is chromatographed on silica gel, eluting with 25:1 $CHCl_3$-EtOAc, providing 1-tosyloxymethyl-3-n-propyl-4-p-nitrophenylthio-azetidin-2-one.

EXAMPLE 17

1-Tosyloxymethyl-3-n-propyl-4-p-nitrophenylsulfinyl azetidin-2-one

1-Tosyloxymethyl-3-n-propyl-4-p-nitrophenylsulfinylazetidin-2-one, 450 mg, is treated for 1 2 hour in 10 ml CH_2Cl_2 with 172 mg m-chloroperbenzoic acid. The solution is washed with aqueous K_2HPO_4, dried with $MgSO_4$, filtered and evaporated, leaving pure 1-tosyloxymethyl-3-n-propyl-4-p-nitrophenylsulfinyl azetidine-2-one.

EXAMPLE 18

1-Acetoxymethyl-4-p-nitrophenylsulfinyl-3-n-propylazetidin-2-one

Step A: Preparation of 3-n-propyl-4-p-nitrophenylthioazetidin-2-one

3-n-Propyl-4-acetoxya zetidinone (1.164 g, 6.58 mmole) and 1.02 g (6.58 mmole) p-nitrothiophenol were heated in a tube in the steam bath for 3.5 hours. The reaction mixture was cooled, diluted with 100 ml ethyl acetate, and the organic phase was washed with 100 ml water, 70 ml 1M H_3PO_4 and 3x100 ml saturated

K_2CO_3. The organic phase was dried over magnesium sulfate, filtered, and solvent removed in vacuo to yield 1.53 g of yellow crystals which were chromatographed on a silica gel column in chloroform-ethyl acetate (4:1) to give 359 mg (19%) of 3-n-propyl-4-p-nitrophenylthioazetidin-2-one.
NMR ($CDCl_3$): δ 0.92 (tr, 3H), 1.2-1.6 (br m, 4H), 3.10 (tr, 1H), 4.91 (d, 1H), 7.0 (br s, 1H), 7.50 (d, 2H), 8.20 (d, 2H).

Step BPreparation of 1-Acetoxymethyl-4-p-nitrophenylthio-3-n-propylazetidin-2-one

A mixture of 273 mg (0.94 mmole) azetidinone from Step A, 26.3 mg paraformaldehyde and 178 mg (0.56 mmole) cesium carbonate was stirred in 20 ml dry tetrahydrofuran at ambient temperature 16.5 hours under nitrogen. A mixture of 430 µl pyridine and 2.56 ml acetic anhydride was added to the reaction mixture and the stirring continued 5 more hours. The solvents were removed in vacuo to give 604 mg crude product which was chromatographed on a silica gel flash column in hexane-ethyl acetate 3:1. This gave 102 mg (30%) of 1-acetoxymethyl-4-p-nitrophenylthio-3-n-propylazetidin-2-one.
NMR ($CDCl_3$): δ 1.0 (tr, 3H), 1.2-1.85 (br m, 4H), 2.1 (s, 3H), 3.22 (tr, 1H), 4.95 (d, 1H), 5.18 (ABBA pattern, $J_1 = 30H_3$, $J_2 = 5H_3$, 2H), 7.65 (d, 2H), 8.22 (d, 2H).

Step CPreparation of 1-Acetoxymethyl-4-p-nitrophenylsulfinyl-3-n-propylazetidin-2-one

To a solution of 46 mg (0.127 mmole) azetidinone from Step B in 4 ml CH_2Cl_2 and 4 ml saturated aqueous $NaHCO_3$ was added 27 mg (0.127 mM) 80% m-chloroperbenzoic acid and the reaction mixture stirred vigorously 15 minutes. The phases were separated and the organic phase was dried over $MgSO_4$, filtered and stripped to yield 57 mg crude product which was chromatographed on a 1000 µ silica gel prep TLC plate in chloroform-ethyl acetate 4:1 to yield 15 mg (31%) of 1-acetoxymethyl-4-p-nitrophenylsulfinyl-3-n-propylazetidin-2-one.
NMR ($CDCl_3$): δ 0.93 (tr, 3H), 1.2-1.8 (br m, 4H), 2.1 (s, 3H), 3.55 (tr, 1H), 4.66 (d, 1H), 5.04 (ABBA pattern, $J_1 = 34H_3$, $J_2 = 6H_3$, 2H), 8.2 (d, 2H), 8.52 (d, 2H).

EXAMPLE 19

4-Acetoxy-3-n-propylazetidin-2-one-1-sulfonic acid tetrabutylammonium salt

A solution of 82 mg (0.463 mmole) 3-propyl-4-acetoxy azetidin-2-one in 5 ml pyridine was heated to 80°. 221 Mg (1.39 mmole) sulfur trioxide-pyridine complex was added and the reaction mixture stirred at 80° one hour. It was then poured into 100 ml 0.5M KH_2PO_4 (aqueous) and washed with 2x25 ml CH_2Cl_2. The combined organic washes were backwashed with 25 ml 0.5M KH_2PO_4. 157 Mg (0.463 mmole) Bu_4NHSO_4 was added to the combined aqueous phases. This was extracted with 2x25 ml CH_2Cl_2 and the combined extracts were dried over $MgSO_4$, filtered, and stripped in vacuo to yield 12.4 mg of an oily residue which was chromatographed on a small silica gel column, eluted first with 75 ml hexan /ethyl acetate (3:1) to remove starting material, then with 100 ml ethyl acetate:methanol (4:1) to yield 13 mg (5.7%) 4-acetoxy-3-n-propylazetidin-2-one-1-sulfonic acid tetrabutylammonium salt.
NMR ($CDCl_3$): δ 1.0 (m, 16H), 1.75 (br m, 20H), 2.16 (s, 3H), 2.90 (br s, H), 3.1 (tr, 1H), 3.3 (tr, 8H), 4.08 (br tr, 1H), 6.18 (s, 1H).

EXAMPLE 20

(3R,4S)-1-(benzylaminocarbonyl)-3-ethyl-3-methyl-4-(4-carboxy)phenoxyazetidin-2-one

Step A: Preparation of (3R,4S)-1-t-butyldimethylsilyl-3-methylazetidin-2-one-4-carboxylic acid

To a solution of 27.5 ml of diisopropylamine in 150 ml of THF at -20° C was added 73.5 ml of 2.4N n-butyl lithium in hexane. After 15 minutes, the solution was cooled to -70° C and a solution of 20 gm of (4S)-1-t-butyldimethylsilylazetidin-2-one-4-carboxylic acid in 75 mL of THF was added. The solution was warmed to -20° C for 15 minutes before a solution of 13.5 mL of methyl iodide in 20 mL of THF was added. After 30 minutes at -20 to 0° C, the reaction was diluted with 300 mL of ether and then poured into a mixture of ice and 400 mL of 1N HCl. The layers were separated and the aqueous layer extracted with ether. The ether layers were washed with brine, dried over sodium sulfate and evaporated. The residue was crystallized from hexane to give 12-15 gms of (3R,4S)-1-t-butyldimethylsilyl-3-methylazetidin-2-one-4-carboxylic acid.
NMR ($CDCl_3$): δ .14 (2, 3H), .32 (s, 3H), .91 (d, 3H), .98 (s, 9H), 3.34 (dq, 1H), 3.71 (d, 1H)

Step B: Preparation of (3R,4S)-1-t-butyldimethylsilyl-3-ethyl-3-methylazetidin-2-one-4-carboxylic acid

To a solution of 13 mL of diisopropylamine in 75 mL of THF at -20° C was added 35 mL of 2.4 M n-butyl lithium in hexane. After 15 minutes the solution was cooled to -70° C and a solution of 10 gms of (3R,4S)-1-t-butyldimethylsilyl-3-methylazetidin-2-one-4-carboxylic acid in 50 mL of THF was added. The solution was warmed to -20° C for 15 minutes and a solution of 6.7 mL of ethyl iodide in 10 mL of THF was added. After 30 minutes at -20° to 0° C the reaction was diluted with ether and poured into a mixture of ice and 1 N HCl. The layers were separated and the aqueous layer extracted with ether. The ether layers were each washed with brine, dried over sodium sulfate and evaporated. The residue was crystallized from a minimum amount of hexane to give 8.8 gms of (3R,4S)-1-t-butyldimethylsilyl-3-ethyl-3-methylazetidin-2-one-4-carboxylic acid.
NMR($CDCl_3$): δ .15 (s, 3H), .31 (s, 3H), .98 (s, 9H), 1.04 (t, 3H), 1.22 (s, 3H), 1.78 (q, 2H), 3.94 (s, 1H).

Step C: Preparation of (3R, 4S)-3-ethyl-3-methyl-4-(4-carbo-t-butoxy)phenoxyazetidin-2-one

To a solution of 13.0 gms of (3R, 4S)-1-t-butyldimethylsilyl-3-ethyl-3-methylazetidin-2-one-4-carboxylic acid in 75 mL of DMF and 15 mL of acetic acid under N_2 was added 23 gms of lead tetraacetate. The reaction was heated at 45-50° C for 18 hours and then poured into ice water and extracted into 2 portions of ether. The ether layers were washed with water, dilute sodium bicarbonate solution and brine, dried over sodium sulfate and evaporated to give 13 gm of crude oil containing a mixture of (3R, 4S) and (3R, 4R)-4-acetoxy-3-ethyl-3-methylazetidin-2-one. To this mixture in 50 mL of acetone was slowly added a solution of 14 gms of t-butyl 4-hydroxybenzoate in 50 mL of acetone, 5 mL of water and 29 mL of 2N sodium hydroxide. The reaction was stirred at room temperature for 64 hours and then diluted with water and extracted with 2 portions of ether. The ether layers were washed with brine, dried over sodium sulfate and evaporated. The residue was prep LC'ed with 15-25% ethylacetate:hexanes to give 6.3 gm of the higher R, (4R) ether and 1.5 gm of the desired (3R, 4S)-3-ethyl-3-methyl-4-(4-carbo-t-butoxy)phenoxyazetidin-2-one.
NMR ($CDCl_3$): δ 1.0 (t, 3H), 1.38 (s, 3H), 1.54 (s, 9H), 1.6-2.0 (m, 2H), 5.30 (s, 1H) 6.7 (brs, 1H), 6.78 (d, 2H), 7.90 (d, 2H).

Step D: Preparation of (3R, 4S)-1-(benzylaminocarbonyl)-3-ethyl-3-methyl-4-(4-carbo-t-butoxy)-phenoxyazetidin-2-one

To a solution of 1.5 gm of (3R, 4S)-3-ethyl-3-methyl-4-(4-carbo-t-butoxy)phenoxyazetidin-2-one in 25 mL of methylene chloride was added 1.2 mL of benzyl isocyanate, 1.4 mL of triethylamine and 10 mg of 4-dimethylaminopyridine. The reaction was stirred at room temperature for 16 hours and then evaporated. The residue was flash chromatographed eluting with 10 to 25% EtoAc-Hexane to give 2.3 gm of (3R, 4S)-1-(benzylaminocarbonyl)-3-ethyl-3-methyl-4-(4-carbo-t-butoxy)phenoxy azetidin-2-one.
NMR ($CDCl_3$): δ .98 (t, 3H), 1.36 (s, 3H) 1.50 (s, 9H), 1.62 (m, 1H), 1.84 (m, 1H), 4.42 (d, 2H), 5.64 (s, 1H), 6.80 (brt, 1H), 7.06 (d, 2H), 7.24 (brs, 5H), 7.90 (d, 2H).

Step E: Preparation of (3R, 4S)-1-(benzylaminocarbonyl)-3-ethyl-3-methyl-4-(4-carboxy)phenoxyazetidin-2-one

To 2.3 gms of (3R, 4S)-1-(benzylaminocarbonyl)-3-ethyl-3-methyl-4-(4-carbo-t-butoxy) phenoxyazetidin-

2-one in an ice bath under N_2 was added 5 mL of anisole and then 25 mL of precooled trifluoroacetic acid. After 1.5 hours at 0° C, the volatiles were removed in vacuo without heating and the residue flash chromatographed using hexane, then 15% EtoAc:Hexane, then 1% HoAc in 15% EtoAc:hexanes to give after ether trituration 1.8 gms of (3R, 4S)-1-(benzylaminocarbonyl)-3-ethyl-3-methyl-4-(4-carboxy)-phenoxyazetidin-2-on

NMR ($CDCl_3$): δ 1.03 (t, 3H), 1.46 (s, 3H), 1.66 (m, 1H), 1.94 (m, 1H), 4.50 (d, 2H), 5.76 (s, 1H), 6.9 (brt, 1H), 7.05 (d, 2H), 7.25 (brs, 5H), 7.98 (d, 2H).

EXAMPLE 21

Starting with 3,3-diethyl-4-acetoxyazetidin-2-one as prepared in Scheme (d) followed by displacement of the acetate with the appropriate phenol and acylation of the nitrogen with the corresponding chiral isocyanate as shown in Scheme (h) and example 20, steps C-E, the following compounds were prepared. The diastereomers obtained on acylation were separated by silica gel chromatography using 10-30% ethylacetate/hexane solvent mixtures.

(4S)-3,3-diethyl-1-((R)-α-ethylbenzylaminocarbonyl)-4-(4-carboxymethyl)phenoxyazetidin-2-one.

NMR ($CDCl_3$):δ 0.9 (t,3H,J = 7Hz), 0.94 (t,3H,J = 7Hz), 1.07 (t,3H,J = 7hz) 1.65 - 2.05 (m,6H), 3.58 (s,2H), 4.8 (q,1H, J = 8Hz), 5.58 (s,1H), 7.0 (d, 1H, J = 8Hz), 7.1 - 7.45 (m,9H)

(4S)-3,3-diethyl-1-((R)-α-n-propylbenzylaminocarbonyl)-4-(4-carboxymethyl)phenoxyazetidin-2-one.

NMR ($CDCl_3$): δ 0.91 (t,3H,J = 7Hz), 0.94 (t,3H,J = 7Hz), 1.07 (t,3H,J = 7hz) 1.34 (m,2H), 1.65 -2.05 (m,6H), 3.57 (s,2H), 4.88 (q, 1H, J = 7Hz), 5.58 (s,1H), 7.0 (d, 1H, J = 7Hz) 7.1 - 7.5 (m, 9H)

(4S)-3,3-diethyl-1-((R)-α-allyl-(4-methyl)benzylaminocarbonyl)-4-(4-carboxymethyl)phenoxyazetidin-2-one.

NMR ($CDCl_3$): δ 0.96 (t,3H,J = 7Hz), 1.07 (t,3H,J = 7Hz), 1.7 - 2.1 (m, 4H), 2.32 (s, 3H), 2.57 (t,2H, J = 7Hz), 3.58 (s, 2H), 4.95 (q, 1H, J = 7Hz), 5.14 (m, 2H), 5.58 (s, 1H), 5.66 (m, 1H), 7.03 (d, 1H, J = 7Hz), 7.16 (s, 4H), 7.19 (s, 4H).

(4S)-3,3-diethyl-1-((R)-α-allyl(3,4-methylenedioxy)benzylaminocarbonyl)-4-(4-carboxymethyl)-phenoxyazetidin-2-one.

NMR ($CDCl_3$): δ 0.96 (t,3H,J = 7Hz), 1.05 (t,3H,J = 7Hz), 1.65 - 2.05 (m, 4H), 2.54 (t, 2H J = 6Hz) 4.87 ((q, 1H, J = 7Hz), 5.05 -5.2 (m, 2H), 5.58 (s, 1H), 5.66 (m, 1H), 5.94 (s, 2H), 6.76 (s, 3H), 6.98 (d, 1H, J = 7Hz), 7.2 (m,4H)).

(4S)-3,3-diethyl-1-((R)-α-n-propyl(3,4-methylenedioxy)-benzylaminocarbonyl)-4-(4-carboxymethyl)phenoxy-azetidin-2-one.

NMR ($CDCl_3$): δ 0.9 (t,3H,J = 7Hz), 0.94 (t,3H,J = 7Hz), 1.06 (t, 3H J = 7Hz), 1.3 (m, 2H), 1.65 -2.1 (m, 6H), 3.58(s, 2H), 4.76(q, 1H, J = 7hz), 5.58(s, 1H), 5.92 (s,2H), 6.15 (s, 3H) 6.88 (d, 1H, J = 7Hz), 7.2 (m, 4H).

(4S)-3,3-diethyl-1-((R)-α-n-propyl(4-methyl)benzylaminocarbonyl)-4-(4-carboxy)phenoxyazetidin-2-one.

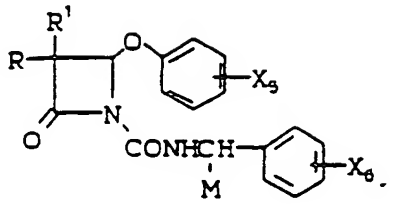
NMR ($CDCl_3$): δ 0.91 (t,3H,J = 7Hz), 0.98 (t,3H,J = 7Hz), 1.07 (t, 3H, J = 7Hz) 1.32 (m, 2H), 1.65 - 2.1 (m, 6H), 2.33(s, 3H), 4.83(q, 1H, J = 7hz), 5.71(s, 1H), 6.93 (d, 1H, J = 7Hz), 7.16 (s, 4H), 7.25 (d,2H,J = 8Hz), 8.04 (d, 2H, J = 8Hz).

(4S)-3,3-di thyl-1-((R)-α-n-propyl(4-methyl)benzylaminocarbonyl)-4-(4-carboxymethyl)phenoxyazetidin-2-one.

NMR ($CDCl_3$): δ 0.9 (t,3H,J = 7Hz), 0.93 (t,3H,J = 7Hz), 1.07 (t, 3H, J = 7Hz) 1.28 (m, 2H), 1.7 -2.1 (m, 6H), 2.33(s, 2H), 3.6 (s,2H), 4.81 (q, 1H, J = 7hz), 5.56 (s, 1H), 6.93 (d, 1H, J = 7Hz), 7.15 (s, 4H), 7.2 (s, 4H).

Claims

1. A compound of the formula (A)



(A)

wherein:
R and R^1 independently are C_{1-6} alkyl or C_{1-6} alkoxy C_{1-6} alkyl;
M is
(1) hydrogen,
(2) C_{1-6} alkyl,
(3) C_{2-6} alkenyl, or
(4) C_{1-6} alkoxy C_{1-6} alkyl;
X_5 is
(1) hydrogen,
(2) C_{1-6} alkyl,
(3) halo C_{1-6} alkyl,
(4) C_{2-6} alkenyl,
(5) C_{2-6} alkynyl,
(6) carboxy,
(7) carboxy-C_{1-6} alkyl,
(8) carboxy-C_{1-6} alkylcarbonyl,
(9) carboxy-C_{1-6} alkylcarbonylamino,
(10) carboxy-C_{2-6} alkenyl,
(11) hydroxy-C_{1-6} alkyl,
(12) C_{1-6} alkylcarbonyl,
(13) C_{1-6} alkylcarbonylamino, or
(14) di-(C_{1-6}alkyl)amino-C_{1-6}alkyl; and
X_6 is
(1) hydrogen,
(2) C_{1-6} alkyl,
(3) halo
(4) carboxy,
(5) C_{1-6} alkoxy,
(6) phenyl,
(7) C_{1-6} alkylcarbonyl,
(8) di-(C_{1-6}alkyl)amino,
(9) phenoxy,
(10) methylenedioxy,
(11) 2,3-furanyl, or
(12) 2,3-thienyl; or
a pharmaceutically acceptable salt thereof.

2. A compound of Claim 1 wherein:
R and R^1 independently are C_{1-6} alkyl;
and
X_5 is carboxy or carboxy-C_{1-6} alkyl.

3. A compound of Claim 2 wherein:
M is C_{1-3} alkyl or allyl; and
X_6 is hydrogen, C_{1-6} alkyl, or 3,4-methylenedioxy or phenyl.

4. A compound of Claim 3 wherein:
R is ethyl; and
R^1 is methyl or ethyl.

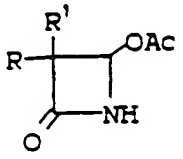
5. A compound of Claim 4 wherein:
R and R^1 are ethyl;
M is n-propyl;
X_5 is 4-carboxymethyl; and
X_6 is 4-methyl.

6. A pharmaceutical composition for the inhibition of human leukocyte elastase which comprises a nontoxic therapeutically effective amount of a compound of Claim 1 and a pharmaceutically acceptable carrier.

7. A composition of Claim 6 wherein:
R is ethyl;
R^1 is methyl or ethyl;
M is C_{1-3} alkyl or allyl;
X_5 is carboxy or carboxy-C_{1-5} alkyl;
and
X_6 is hydrogen C_{1-5} alkyl, 3,4-methylenedioxy or phenyl.

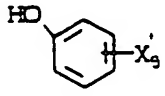
8. A composition of Claim 7 wherein:
R^1 is ethyl;
M is n-propyl;
X_5 is 4-carboxymethyl; and
X_6 is 4-methyl.

9. A process for the preparation of the compounds of Claim 1 which comprises
(1) reacting a compound of the following formula (B)



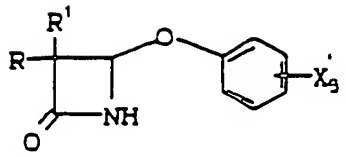
(B)

with a compound of the formula (C)



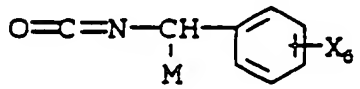
(C)

wherein X_5' is
(1) hydrogen
(2) C_{1-5} alkyl,
(3) halo-C_{1-5} alkyl,
(4) C_{2-5} alkenyl,
(5) C_{2-5} alkynyl,
(6) C_{1-5} alkoxycarbonyl,
(7) C_{1-5} alkoxycarbonyl-C_{1-5} alkyl,
(8) C_{1-5} alkoxycarbonyl-C_{1-5} alkylcarbonyl,
(9) C_{1-5} alkoxycarbonyl-C_{1-5} alkylcarbonylamino,
(10) C_{1-5} alkoxycarbonyl-C_{2-5} alkenyl,
(11) hydroxyalkyl,
(12) C_{1-5} alkylcarbonyl,
(13) C_{1-5} alkylcarbonylamino, or
(14) di-(C_{1-5} alkyl)amino-C_{1-5} alkyl under basic conditions to afford a compound of the formula (D)



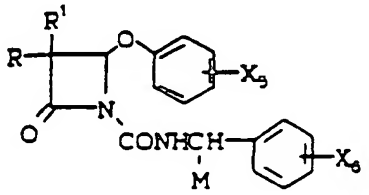
(D)

and (2) reacting compound (D) with a compound of the formula (E)



(E)

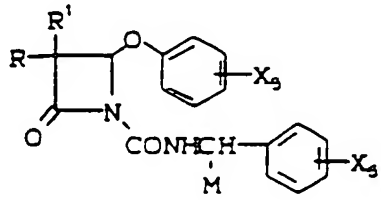
under basic conditions, and optionally converting X_5' into X_5, to yield the compound of the formula (A)



(A).

10. A process of Claim 9 wherein:
Step (1) is in the presence of an alkali metal hydroxide.
Ste (2) is in the presence of a tri(C_{1-5} alkyl)-amine; and
the conversion of X_5' into X_5 is accomplished in the presence of a strong acid.
Claims for the following Contracting States: ES and GR

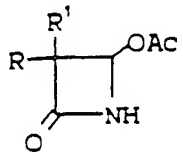
1. A process for the preparation of a compound of the formula (A)



(A)

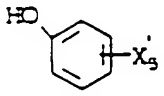
wherein:
R and R^1 independently are C_{1-5} alkyl or C_{1-5} alkoxy C_{1-5} alkyl;
M is
(1) hydrogen,
(2) C_{1-5} alkyl,
(3) C_{2-5} alkenyl, or
(4) C_{1-5} alkoxy-C_{1-5} alkyl;
X_5 is
(1) hydrogen,
(2) C_{1-5} alkyl,
(3) halo C_{1-5} alkyl,
(4) C_{2-5} alkenyl,
(5) C_{2-5} alkynyl,
(6) carboxy,
(7) carboxy-C_{1-5} alkyl,
(8) carboxy-C_{1-5} alkylcarbonyl,
(9) carboxy-C_{1-5} alkylcarbonylamino,

(10) carboxy-C_{2-5} alkenyl,
(11) hydroxy-C_{1-5} alkyl,
(12) C_{1-5} alkylcarbonyl,
(13) C_{1-5} alkylcarbonylamino, or
(14) di-(C_{1-5}alkyl)amino-C_{1-5}alkyl; and
X_5 is
(1) hydrogen,
(2) C_{1-5} alkyl,
(3) halo
(4) carboxy,
(5) C_{1-5} alkoxy,
(6) phenyl,
(7) C_{1-5} alkylcarbonyl,
(8) di-(C_{1-5}alkyl)amino,
(9) phenoxy,
(10) methylenedioxy,
(11) 2,3-furanyl, or
(12) 2,3-thienyl; or
a pharmaceutically acceptable salt thereof which comprises
(1) reacting a compound of the following formula (B)



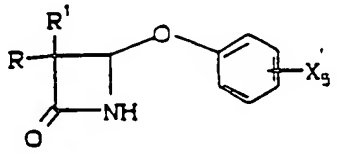
(B)

with a compound of the formula (C)



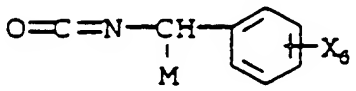
(C)

wherein X_5' is
(1) hydrogen
(2) C_{1-5} alkyl,
(3) halo-C_{1-5} alkyl,
(4) C_{2-5} alkenyl,
(5) C_{2-5} alkynyl,
(6) C_{1-5} alkoxycarbonyl,
(7) C_{1-5} alkoxycarbonyl-C_{1-5} alkyl,
(8) C_{1-5} alkoxycarbonyl-C_{1-5} alkylcarbonyl,
(9) C_{1-5} alkoxycarbonyl-C_{1-5} alkylcarbonylamino,
(10) C_{1-5} alkoxycarbonyl-C_{2-5}alkenyl,
(11) hydroxyalkyl,
(12) C_{1-5} alkylcarbonyl,
(13) C_{1-5} alkylcarbonylamino, or
(14) di-(C_{1-5} alkyl)amino-C_{1-5} alkyl
under basic conditions to afford a compound of the formula (D)



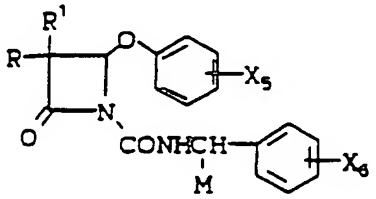
(D)

and (2) reacting compound (D) with a compound of the formula (E)



(E)

under basic conditions, and optionally converting X_5' into X_5, to yield the compound of the formula (A)



(A)

2. A process of Claim 1 wherein:
R and R^1 independently are C_{1-6} alkyl; and
X_5 is carboxy or carboxy C_{1-6} alkyl.

3. A process of Claim 2 wherein:
M is C_{1-3} alkyl or allyl; and
X_6 is hydrogen, C_{1-6} alkyl, or 3,4-methylenedioxy or phenyl.

4. A process of Claim 3 wherein:
R is ethyl; and
R^1 is methyl or ethyl.

5. A process of Claim 4 wherein:
R and R^1 are ethyl;
M is n-propyl;
X_5 is 4-carboxymethyl; and
X_6 is 4-methyl.

6. A process of Claim 1 wherein:
Step (1) is in the presence of an alkali metal hydroxide;
Step (2) is in the presence of a tri(C_{1-5} alkyl)amine; and
the conversion of X_5' into X_5 is accomplished in the presence of a strong acid.

European Patent Office

EUROPEAN SEARCH REPORT

Application number

EP 89200864.0

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X	EP - A1 - 0 199 630 (MERCK) * Claims 1,9 *	1-9	C 07 D 205/08 A 61 K 31/395

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

C 07 D 205/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	14-07-1989	JANISCH

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO Form 1503 03.82